THE EMERGENCY DIAGNOSIS OF ACUTE ISCHEMIC BOWEL

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ABSTRACT

THE EMERGENCY DIAGNOSIS OF ACUTE ISCHEMIC BOWEL. John A. Thompson, Linda C. Degutis, Christopher C. Baker. Section of General Surgery, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

The well-known difficulty of obtaining an early diagnosis of acute ischemic bowel must be overcome to insure prompt life-saving intervention. The records of 49 patients with acute intestinal ischemia admitted to Yale-New Haven Hospital through the Emergency Service over a seven year period (1981-1987), was compared to a matched control group of 94 patients with other abdominal conditions, in order to define those signs, symptoms, laboratory, physical and radiographic findings that may be aids to prospective diagnosis of intestinal ischemia. A combination of sudden, severe, crampy, generalized abdominal pain accompanied by nausea and vomiting was the most frequent presentation in patients with ischemic bowel. Additionally, many patients demonstrated decreased serum bicarbonate, elevated glucose, and an amylase elevated out of proportion to lipase. Multiple air/fluid levels and dilated loops of small bowel were common on plain film diagnosis of the abdomen. While none of these findings is in itself specific for ischemic bowel, the combination of severe abdominal pain accompanied by any of the above should raise the level of suspicion of ischemia enough to warrant further

radiographic studies. Lack of clinical suspicion, use of narcotic pain-killers, and confounding illness in the aged patient all contributed significantly to delayed diagnosis. A discriminant function was generated that had a within study predictive value of 71%.

DEDICATION

To Keith - for his extraordinary understanding, support, and patience; but most of all for just being there.

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INTRODUCTION

In the 146 years since Tiedmann[21] first described a case of mesenteric vascular occlusion, much has been written on both its diagnosis and treatment. Sadly, since Elliot[22] first successfully operated on a case of intestinal gangrene in 1895 and demonstrated that early intervention can be curative, hundreds, if not thousands, of people have died of this very condition as a result of the inability to identify it and to intercede in a timely manner. Recent figures estimate that as many as 50% of patients with ischemic bowel have not been given a correct ante-mortem diagnosis.[6,33]

Of the many different causes of intestinal ischemia, all have in common either a vascular or hemodynamic inability of the body to adequately perfuse the gut. The clinical spectrum ranges from a relatively minor and reversible functional alteration of the intestinal mucosa to a massive hemorrhagic infarction of the entire bowel carrying with it a lethal prognosis.

Ischemic bowel has been classified in a number of ways by its underlying cause and by the size and location of the insult. The underlying causes are generally divided into four major categories:

1) Arterial thrombosis
2) Arterial embolism
3) Mesenteric venous occlusion
4) Non-occlusive

Lesions may affect major portions of the small intestine and/or the large intestine or they may be of limited size and classified as the focal/segmental type. The underlying causes of focal/segmental ischemia are much more varied and will be presented later. Although colonic ischemia is seen with approximately the same frequency as ischemia of the small intestine, most cases are far less injurious and usually do not require significant intervention. Additionally, the syndrome of chronic bowel ischemia or "abdominal angina" has been described in the literature. Although it is now believed to be less frequent than once thought, it may be significant as a risk factor for later acute mesenteric infarction.[27]

This study will confine itself to the more serious portion of the spectrum of intestinal ischemia: patients with acute small bowel infarction, either massive or focal/segmental, who require immediate diagnosis and intervention. Retrospective analysis was performed on the history, signs, and symptoms of 50 of these patients who presented to the Emergency Service of Yale-New Haven Hospital between the years 1981 and 1987. A matched control group of 100 patients with other acute abdominal conditions formed the basis of comparison used in determining what factors, if any, alone or in combination, were discriminating for making an early diagnosis of acute intestinal ischemia.

REPORT OF TWO CASES

Case 1

A 73-year-old white female was admitted with a 72-hour history of sudden onset of severe crampy abdominal pain accompanied by nausea, vomiting, and diarrhea. She had been seen and released by her primary physician on the day that the symptoms began with a diagnosis of viral gastroenteritis and was given a prescription for codeine. She had previously enjoyed excellent health with a history significant only for non-insulin dependent diabetes mellitus. Her last bowel movement was 48 hours prior to admission. The physical examination revealed a pulse of 96, blood pressure of 170/90 and a temperature of 100°F. The abdomen was silent and diffusely tender without guarding or rebound. The lungs were clear. Rectal exam revealed heme positive stool. Hematocrit (42) was normal. Leukocytes (20,400) were elevated with 43 segs, 42 bands, and 12 lymphs. Arterial blood gas had a pH of 7.46, pCO_2 24, pO_2 74. Electrocardiogram(EKG) was remarkable for new onset atrial fibrillation. KUB demonstrated multiple air/fluid(A/F) levels, distended small bowel and several phleboliths. The patient was admitted for observation. Exploratory laparotomy was performed 48 hours after admission and revealed massive unresectable gangrene of the small intestine from the ligament of Treitz to the transverse colon. Post-operative diagnosis was infarction of the small bowel secondary to arterial embolization. The patient died two days later.

Case 2

A 60-year-old black male was admitted with a 6-hour history of sudden onset severe crampy abdominal pain accompanied by nausea and vomiting. He had a history significant for hypertension and an episode of thrombophlebitis 2 years prior to admission. His last bowel movement was 36 hours prior to admission. The physical examination revealed a pulse of 60, blood pressure of 140/palp and a temperature of 100^{2}°F. The abdomen was silent and diffusely tender in the lower quadrants with mild rebound. The lungs were clear. Rectal exam revealed heme negative stool. Hematocrit (46.7) was normal. Leukocytes (18,400) were elevated with 81 segs, 5 bands, and 7 lymphs. EKG was remarkable for a left anterior hemi-block. KUB demonstrated two A/F levels, small intraintestinal air pockets, and several phleboliths in the lower pelvis. Exploratory laparotomy was performed 3 hours after presentation and resulted in resection of over 80% of the small bowel. Post-operative diagnosis was diffuse hemorrhagic infarction of the small bowel without evidence of arterial or venous occlusion. The patient was discharged one month later after recovering from a secondary wound dehiscence and is alive and well two years later having experienced only a few minor digestive difficulties secondary to short bowel syndrome.

Discussion

Neither of these cases is an atypical presentation of ischemic bowel; a patient, suffering from severe, crampy abdominal pain of sudden onset, seeks prompt medical attention. Yet the outcomes of each case are dramatically different. Just as time plays a critical role in the medical management of acute coronary ischemia, time is precious in the diagnosis and subsequent surgical intervention of acute intestinal ischemia. Could it have been that the woman in Case 1 appeared to be in less distress than the man in Case 2 causing the latter patient to receive prompt life-saving intervention? Or was it perhaps a combination of the training and clinical experience of the second physician that raised the suspicion of the diagnosis of ischemic bowel? The laboratory values of the patients do not, at a casual glance, appear to be necessarily revealing of a life-threatening pathological process. A similar leukocytosis could be secondary to a far less serious viral condition. The signs of bowel obstruction on the abdominal films might be a bit worrisome to some, and the new onset atrial fibrillation does raise the possibility of embolic phenomena. Why then was the 73 year old female observed, on codeine, for 48 hours in the hospital while 3 hours after presentation the 60 year old male was undergoing a massive bowel resection? Perhaps there are several factors, either those presented here or factors not yet mentioned, the combination of which would indicate a

patient at significant risk. Clearly, these cases represent prototypes of the actual presentation of patients with intestinal infarction. Yet, they demonstrate the common difficulty faced by the physician in rapidly and definitively diagnosing a disease which is universally fatal if left untreated. This study will address itself to identifying, and perhaps explaining, those signs and symptoms, or combinations thereof, that are particularly discriminating for the early diagnosis of acute intestinal ischemia.

LITERATURE REVIEW

Overview

Incidence

While several studies since the early sixties have reported a significant increase in the incidence of acute ischemic bowel, this disease is roughly estimated to account for between 5 and 10 hospital admissions per 100,000.[6,7,31] Boley & Brandt[17] report the highest incidence of all ischemic intestinal conditions, as high as 1 per 1,000 admissions during the 1970's, at Montefiore Hospital in New York. They attribute this figure to the combination of an aging population and increased recognition of the condition during their studies.[17]

Statistics on the relative incidences of the causes of small bowel infarct vary widely from study to study. A tabulation of 1,500 cases by Jackson[29] in 1963 found 26% due to emboli, 24% arterial thrombosis, 33% venous occlusion, and 12% infarct without vascular evidence (non-occlusive). More recent studies have placed the incidence of non-occlusive disease as high as 70% of all cases and the incidence of venous occlusion as low as 8%.[2,17] Boley,[27] on the other hand, reports a relative decrease between 1970 and 1977 of non-occlusive cases and speculates that the underlying reason is secondary to improved hemodynamic maintenance of patients

with atherosclerotic disease by a decrease in dependency on preload reducers, such as digitalis, and a pharmacological shift to afterload reduction.

Mortality

Mortality figures, while varying with the underlying cause of the ischemic insult, have seen little decrease over the past several decades. Acute occlusion generally carries a mortality rate of as high as 90%[13] although prompt intervention can lower that figure to as low as 30%.[2] The current treatment of non-occlusive disease, however, has been relatively unsuccessful in lowering its mortality rate of 90%.[17] This may be due not only to a delay in its diagnosis and intervention, but also to the inability of surgery to address the underlying causes of non-occlusive disease in the extremely ill patient. For this reason, other strategies such as pharmacological vasodilatation are being investigated as both a first-line treatment and an adjuvant to surgical resection.[17] In a study by Sullivan[2], mortality rates for other causes of ischemia range from as low as 20% for venous thrombosis to upwards of 60% for arterial thrombosis.

One reason for the high mortality figures across the spectrum of ischemic bowel include its prevalence in an aged and debilitated patient population already possessing a variety of other underlying diseases. These confounding factors not only make the diagnosis more difficult, but add

to the risk of surgery and decrease the body's ability to deal with the pathological insult that accompanies intestinal infarction.

Pathophysiology

To better understand the entire spectrum of mesenteric ischemic disease, the blood supply to the normal intestine will be reviewed, followed by an examination of the pathophysiology of the various types of bowel infarction commonly described in the literature.

Splanchnic Vasculature

Anatomy texts describe the extensive blood supply to the digestive system and detail the numerous collateral channels between the three major splanchnic outlets of the aorta: the celiac axis, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA).

The celiac axis, which divides into the splenic, hepatic, and left gastric arteries, supplies the upper potion of the GI tract from the stomach through the ligament of Treitz. Of the two branches of the hepatic artery, the right gastric and gastroduodenal arteries, the latter gives rise to the superior pancreaticoduodenal artery, which, although small, may form an important anastomosis with the inferior pancreaticoduodenal branch of the SMA. The splenic artery also forms an important anastomosis with the SMA through the dorsal pancreaticoduodenal artery.

The SMA supplies the greater part of the intestinal tract from the distal portion of the duodenum to the transverse

colon by way of several branches: the inferior pancreatico-duodenal, intestinal, middle, right and ileocolic arteries. The three colic vessels converge to form an anastomosis with the IMA through the marginal artery.

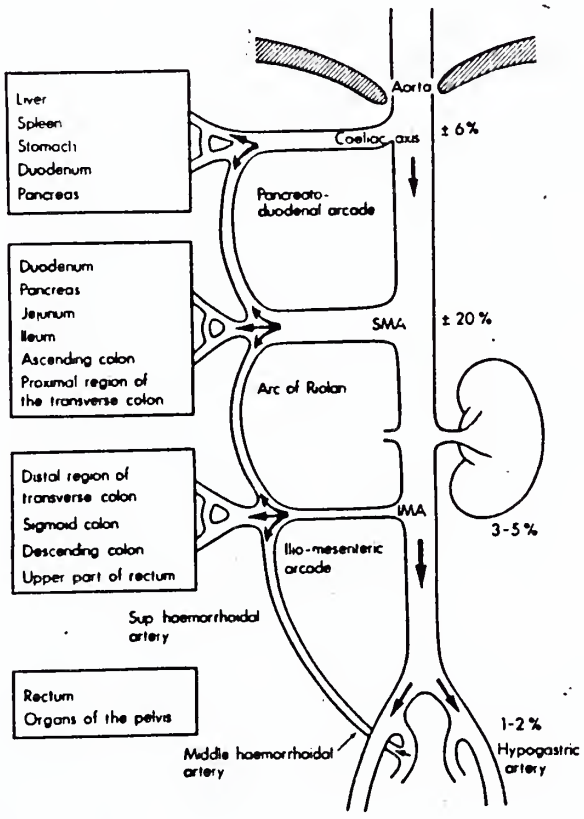
The IMA, arising proximally to bifurcation of the aorta, nourishes the remainder of the colon and rectum. Distally, the anastomosis which it forms with the internal iliac arteries is responsible in some patients for the "aorto-iliac steal syndrome" described below.[18] Due to its heavy collateralization, blood flow through the IMA is frequently compromised in many individuals with little or no sequelae.[2]

A general rule is that circulation in two of the three main vessels must be compromised to result in inadequate perfusion to any portion of the intestine. Acute obstruction, however, of either the celiac trunk or the SMA, in patients who have not developed adequate collateralization over time, may result in severe ischemia.[18] Ligation of the IMA, as may be done in a colectomy, seldom causes a problem but may put patients at risk of future ischemia because such ligation eliminates important collaterals of the SMA.[18]

Measurements of the specific contributions of the various arteries to splanchnic blood flow has been accomplished by several methods. Both the dye dilution technique and angiographic spill-over technique[46] estimate that the SMA carries from 360-1200 ml/minute with an average of 700ml/minute.[5] The

video dilution technique verifies that this measurement is between 11% and 20% of resting cardiac output,[5] thereby demonstrating the relative significance of the SMA in comparison to the celiac trunk and IMA (Figure 1).[19] These measurements increase on the average of 100% after a solid meal and approximately 63% after a liquid meal.[5] It is the sympathetic nervous system which exerts the greatest control over splanchnic circulation by means of vasoconstricting α-andrenergic receptors. Parasympathetics are felt to play a relatively minor role in the control of mesenteric blood flow.[17]

Figure 1 - Principal Splanchnic Vessels[18]



In addition to major arterial anastomoses, the bowel provides its own internal collateralization through the primary, secondary, and tertiary arcades.[17] Such collateral pathways open immediately in response to a drop in arterial pressure distal to an obstruction in another portion of the bowel.[17] Furthermore, since at any one time only one fifth of mesenteric capillaries are open, they may also provide a significant reserve of collateralization when called upon.[17]

Emboli to the SMA

According to recent estimates, emboli to the SMA account for approximately 40-50% of episodes of acute intestinal ischemia.[27] Although the most common origin of such emboli are mural or atrial thrombi in patients with a history of arteriosclerotic heart disease, atrial fibrillation and rheumatic heart disease are also closely correlated with embolization.[4,27] Thirty-three percent of the patients in one study had a previous history of systemic emboli.[4]

The ostium of the SMA, at its take-off point from the aorta, is oblique and provides a favorable entry for emboli. In contrast, the celiac axis leaves the aorta at a right angle and is rarely the site of embolic occlusion.[18] Characteristically, emboli tend to lodge at arterial bifurcations; the junction of the middle colic artery is the favored site 55% of the time. Other common sites are the SMA origin (18%), right colic artery (16%), and ileocolic artery (7%).[17] In most

patients, lack of collateralization will result in irreversible damage within 6 hours, especially if the embolus is lodged distal to the junction of the mid colic artery.[4,18]

Acute occlusion of the SMA is generally associated with sudden onset of abdominal pain and a rapid emptying of the intestine.[18] It is a very rare patient who survives an acute embolus without intervention; immediate surgical embolectomy, followed by resection of nonviable bowel, is by far and away the treatment of choice.[4]

Thrombosis of the SMA

Thrombosis of the SMA is a disorder associated with underlying arteriosclerotic peripheral vascular disease. A gradual and progressive narrowing of the lumen of the SMA, usually near its origin, is not infrequently accompanied by a history of weeks or months of diffuse, intermittent abdominal pain. Brandt, et al.[27] report a history of antecedent abdominal angina in 30-50% of patients diagnosed with acute SMA thrombosis. Since the progressive onset of the disease allows time for many patients to develop substantial collateral circulation, Brandt also points out the necessity of differentiating an acute occlusion from a long-standing one when interpreting an abdominal angiography.[27] In the absence of adequate collateralization an acute occlusion is generally presumed and surgical intervention, along with pharmacological vasodilatation, is indicated.[27] Although very uncommon,

arterial thrombosis may also occur at sites other than the origin of the SMA. Moreover, thrombosis may play a contributory role in non-occlusive intestinal ischemia (see next section) by compromising the arterial supply prior to a "low-flow" state.

Venous Occlusion (MVT)

Once thought to play a large role in acute intestinal ischemia, mesenteric venous thrombosis (MVT) is more recently reported to account for as few as 8% of all cases.[2] Others contend that minor cases of MVT are much more common and simply go unreported because of the paucity of significant clinical manifestations.[15] The syndrome, unlike other forms of ischemia, is most commonly reported in persons between the ages of 50 and 70.[15] Predisposing hypercoagulable states have been implicated in the pathogenesis of MVT and include post-splenectomy syndrome (platelets>1,000,000), polycythemia rubra vera, and use of birth control pills.[13] Additionally, cirrhotic patients with portal hypertension and patients with focal abdominal infection or renal failure are at increased risk.[18,28]

The manifestations of severe mesenteric venous occlusion parallel those of arterial occlusion and include significant fluid loss, low grade fever, significant abdominal pain, and end stage peritonitis.[15] Standard diagnostic studies are unable to discriminate MVT from other ischemic insults

although reports of mesenteric blush on liver-spleen scan[15] and detection of stasis in the superior mesenteric vein by ultrasound[39] may prove useful after further investigation. Angiography, as might be expected, is generally normal in these individuals.[27]

Surgery is indicated for patients with intestinal infarction secondary to MVT and anticoagulation with heparin and coumadin has been shown to increase the survival rate from 65% to 77% after the operation.[15,18] Despite such measures, the mortality rate in general for MVT has only fallen by 12% between 1911 and 1984.[15]

Non-Occlusive Intestinal Ischemia

Ende[35] first described non-occlusive intestinal ischemia in 1958 as a phenomenon secondary to hypoperfusion of the gut following cardiac failure. It is now said to account for upwards of 50% of all reported cases.[27,31] Patients with myocardial infarction, CHF, aortic insufficiency, renal or hepatic disease, or major abdominal or cardiac surgery are all at increased risk for this condition.[17] The common link between all of the predisposing conditions is a reflexive splanchnic vasoconstriction in response to decreased cardiac output, hypovolemia, dehydration, drugs, or hypotension.[17] One drug of note, digitalis, has been frequently implicated in non-occlusive ischemia because of its vasoconstrictive action on the splanchnic arteries.[2] Pierce[28] reports 90% of non-

occlusive patients in his study were on digitalis in comparison to 60% in his control group, although the severity of cardiac failure in both groups was similar.

A study by Wittenberg, et al.[6] demonstrated that the presenting symptoms of 21 patients, both prospectively and retrospectively, did not vary significantly between non-occlusive and occlusive ischemic bowel disease. Unlike acute arterial obstruction, however, the gangrene that develops is focal and dispersed among normal areas of bowel. These focal areas are not segmental and, thus, do not follow a specific vascular distribution.[36]

Therapy consists of a combination of surgical and pharmacological maneuvers, the latter being a local infusion of vasodilating drugs such as papavarine or tolazoline.[17,36] Mortality figures for non-occlusive disease are uniformly high, about 90%[17], and may reflect the range of serious underlying conditions that accompany this diagnosis.

Focal Segmental Ischemia

Focal segmental ischemia, as the name reveals, is an ischemic lesion localized to a short portion (focus) of the bowel with a definable (segmental) vascular supply. This category carries with it a broad range of etiologies and a wide variety of clinical presentations. Frequent causes include small artheromatous emboli, strangulated hernias, collagen diseases, blunt abdominal trauma, segmental venous

thrombosis, and enteric coated thiazide-potassium chloride tablets.[27] Due to the limited size of the lesions, there is usually sufficient collateral circulation to prevent a transmural hemorrhagic infarct, hence the usual lesion consists of a superinfected partial infarction of the mucosal and muscular layers of the small intestine.[17] The virulence of such secondary infections is directly related to the outcome of the patient and, therefore, the better prognosis is given to lesions further away from the highly toxigenic bacteria of the colon.[17] Focal segmental ischemia frequently results in strictures of the small intestine when the insult penetrates below the mucosal layer and invades the muscularis.[17]

Brandt, et al.[27] have divided the common presentations into three main categories. The acute attack mimics appendicitis, and presents with sudden onset of severe abdominal pain. The transmural nature of the infarct often leads, in time, to the frank peritoneal signs of an abdominal catastrophe. The second group of patients presents with the symptoms of chronic enteritis (crampy pain, diarrhea, fever) and is often indistinguishable clinically from Crohn's disease. The third, and most common, group defined by Brandt is the presentation of small bowel obstruction often as the result of stricture formation.[17]

The treatment of focal segmental ischemia is directed at the specific nature of the lesion and is most often surgical. Unlike the other forms of acute intestinal ischemia, some

patients are adequately managed without surgery on a "watch and wait" basis.[17] Mortality figures for this condition vary widely and, while lower than those for other causes, are not appropriately calculated for this group as a whole.

Chronic Ischemia

First described by Schnitzler in 1901, chronic ischemia, or abdominal angina (sometimes referred to as "SMA Syndrome"), is a non-lethal condition involving only the intestinal mucosa.[1,18] It is characterized by post-prandial crampy abdominal pain beginning 10 to 15 minutes after a meal and lasting between 1 and 3 hours.[1,2] Analogous to angina pectoris, the phenomenon is believed to be the result of an increased blood demand by the full intestine in a patient who, often secondary to arterial thrombosis, does not have sufficient circulatory capacity to meet that demand.[18] Generally, it is believed that two vessels must be compromised, often by as much as 86%, in order to reduce blood flow to a point of causing such a mucosal infarction.[2,18] Weight loss is common in these patients secondary to scarring and fibrosis of the intestinal lumen, causing a malabsorption syndrome.[2] Additionally, many patients, fearing the onset of post-prandial pain, actually avoid eating in sufficient quantities for adequate nutrition.[18]

Angiography is indicated to aid in the diagnosis of chronic mesenteric ischemia although it is not always conclusive.[1]

Nevertheless, the occurrence of post-prandial pain may be a precursor to a larger infarction and should warrant a degree of concern from the clinician.[2] Dunphy[37] reported in 1936 that such pain was common in over 50% of patients later dying from SMA thrombosis. For stated reasons, these same patients might do well to avoid digitalis containing preparations. Surgical revascularization is an alternative only in the symptomatic patient, and aorto- arterial bypass graft is the preferred treatment in most cases.[18]

The "aorto-iliac steal syndrome" described by Marston[12] in 1977 is a related condition in which obstruction of the terminal aorta results in blood flow through the SMA and its collaterals, by way of retrograde perfusion of the iliacs, supplying the lower limbs. Thus, the increase in blood supply to the legs on walking comes at the expense of the GI tract.[12]

This study considers exclusively the diagnosis of acute intestinal ischemia and includes chronic ischemia only as it pertains to acute ischemia as a risk factor.

Celiac Compression Syndrome

The celiac compression syndrome is a disorder of questionable etiology, if it exists at all, but is generally believed to be caused by the compression of the celiac axis by the median arcuate ligament of the diaphragm or neurofibrosis of the celiac ganglion.[9] A form of chronic ischemia, it is present most commonly in pre-menopausal females.[9] There has

been much debate as to the very existence of this syndrome, especially considering the adequate collateral circulation in such young people.[12] The celiac compression syndrome will not be considered by this study.

Ischemic Colitis

While ischemic colitis is more common than acute small bowel ischemia, it is generally a much less severe, self limiting disease in over 90% of all cases.[3]

Table I - Differential Diagnosis of Acute Mesenteric Ischemia and Colonic Ischemia[17]

Colonic Ischemia	Acute Mesenteric Ischemia
90% in patients over 60 years	Most in older age group but may occur in younger patients
Acute precipitating cause rare	Acute precipitating cause unusual, e.g., myocardial infarct, congestive heart failure, arrhythmia, hypotension
Predisposing associated lesion present in 20%, e.g., colonic carcinoma, stricture, diverticulitis	Predisposing lesion uncommon (excluding atherosclerosis)
Do not appear seriously ill	*Usually appear ill*
Usually have mild abdominal pain with minimal tenderness and guarding	Pain more severe, findings are minimal early in course, but become more pronounced later
Mild rectal bleeding or bloody diarrhea	Rectal bleeding and diarrhea uncommon until late in the course
Should have barium enema first	*Should have angiography first*

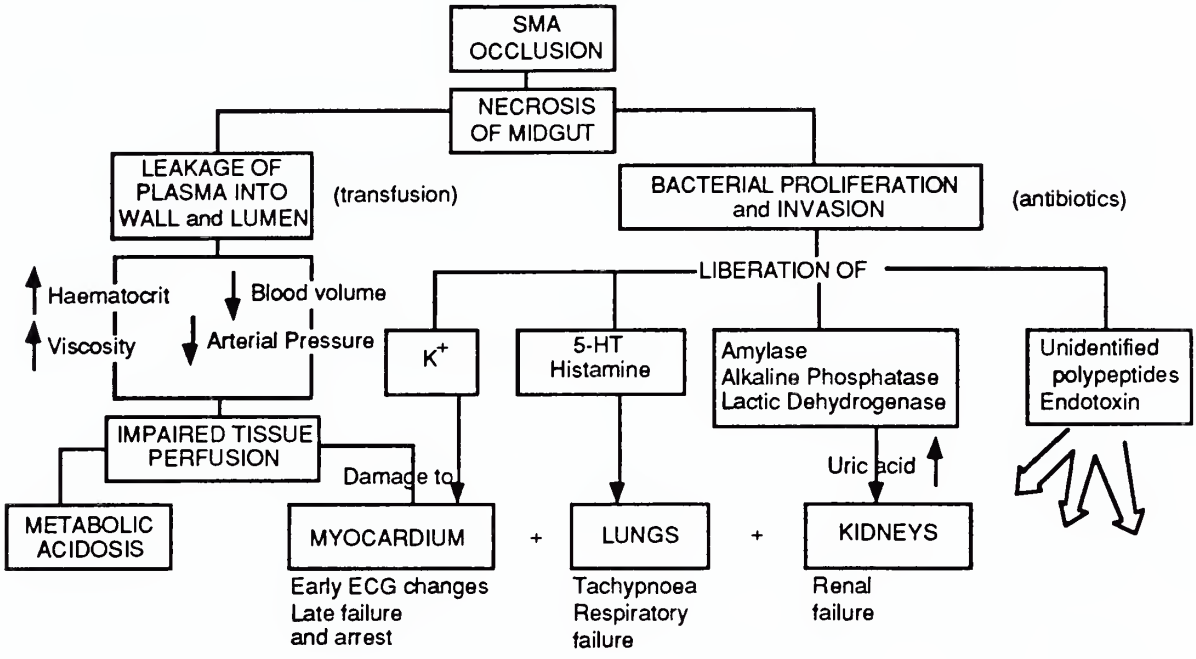
Usually managed by NG suction and antibiotics, only rarely will it progress to a state of gangrenous, life-threatening

necrosis.[3,18] Table I presents a list of discriminating factors between ischemic colitis and small bowel infarction. Patients with ischemic colitis have not been included in this study.

Pathological Changes Accompanying Infarction

Although it takes approximately 6 hours from the onset of ischemia to produce an irreversible mucosal infarction, ultrastructural changes have been demonstrated by electron microscopy after as little as 10 minutes.[2,40] Brown, et al.[40] describe damage to the rough and smooth endoplasmic reticulum after only 10 minutes of intestinal anoxia with reversible failure of basic cell functions, such as mitochondrial O_2 uptake, evident within 30 minutes. The muscular layer is somewhat more resilient to ischemia and demonstrates irreversible damage after approximately 8 hours.[13] Systemically, hypovolemia is noted early on and is the result of a massive loss of H_2O, electrolytes, and plasma into the intestinal lumen.[2,17] This is followed by the appearance of cellular breakdown products such as potassium and the release of certain vasoactive peptides.[2] Metabolic acidosis traditionally follows a sizeable infarction and, over time, elevations have been noted in LDH, SGOT, and CPK.[2,4] Figure 2[41] provides an overview of the sequence of events following an ischemic insult to the gut.

Figure #2 - Effects of Acute Occlusion of SMA



(From Marston. First published in Annals of the Royal College of Surgeons of England, 1972, vol 50, p 32.)

Bacteriologically, as one moves distally (towards the colon) the intestinal flora become more pathogenic.[18] The increase in anaerobic bacteria such as C. difficle or Clostridium type C near and within the colon can cause an extremely virulent superinfection resulting in gas dissections of the intestinal wall as well as gas within the portal venous system.[18] Thus, the severity of the inevitable colonization of the intestinal wall after mucosal shedding is related to the location of the infarction.[18]

Surgical reversal of bowel ischemia, by embolectomy, thrombectomy, or bypass, is successful only if performed within the first 6 to 8 hours before irreversible damage has

occurred. After that point resection is required to remove the offending portion of gut and prevent infection and necrosis. Damage to the mucosal layer alone generally results in reversible desquamation of intestinal villi, while infarction of the muscularis is irreversible and often results in stricture and stenosis.[17,18] Externally, the intestine may appear pink even in the face of a hemorrhagic infarct.[17] Due to a shunting of blood away from the damaged tissue in the distended bowel, this phenomenon underscores the need for careful examination at laparotomy and even a "second-look" procedure later on.[17]

Diagnosis

The diagnosis of acute intestinal ischemia, which is the focus of this study, will be approached by examining the entire clinical picture of the patient's history, physical exam, laboratory tests, and radiological findings. While the definitive diagnosis is often not made until laparotomy, the most discriminant single diagnostic modality to date is the abdominal angiogram. Using angiography, Boley, et al.[27] correctly diagnosed 94% of patients with acute ischemia. This procedure, however, carries with it both a risk and a cost to the patient and is best performed by an experienced radiologist. For this reason it is necessary to determine, in a scientific manner, which patients are to be subjected to angiography because their clinical picture suggests a high relative risk of acute ischemia. Here we examine the observations and results of other experimenters and clinicians who have addressed the issue of early diagnosis.

History

A number of predisposing factors and complicating diseases in the patient's history have been presented by Kaare[6] as they relate to the specific ischemic event and are presented here in Table II.

Table II - Complicating Diseases in 56 Patients[6]

	No. of cases
Fibrillation	24
Cardiac infarction	11
Mitral stenosis	5
Cerebral infarction	6
Cirrhosis	2
Parkinsonism	1
Acromegaly	1
Pulmonary embolism	1
Cholangitis	1
Bronchopneumonia	1
Subacute bacterial endocarditis	1
Carcinoma of the prostate	1

Although several of thew above mentioned conditions are totally unrelated to the ischemic event, the range of different predisposing conditions reflects variegated patient population with intestinal ischemia and also the complexity involved in using such factors as discriminators for the disease. A history of complicating disease has been found in as few as half, and as many as all, of patients in various investigations.[33] But it is apparent that the presence of such factors often does more to cloud the clinical picture, rather than to aid it, as the antemortem diagnosis of ischemic bowel is generally not made in nearly 50% of patients.[6,33]

The Physical Exam - Classic Signs & Symptoms

Abdominal pain out of proportion to the physical exam is perhaps the most commonly recalled finding on physical exam, and likely also the most valuable. The splanchnic nerves of

the autonomic nervous system supply the visceral peritoneum and are responsible for the sensation of pain when the intestine is stretched or anoxic.[14] If originating in the small bowel, this pain will be felt in the periumbilical area through connections to the celiac plexus and then via splanchnic nerves to T6-T9.[14] Distention of the colon produces pain in the hypogastrium through the mesenteric plexus and its connections to T10-T12.[14] Later in the disease, the parietal peritoneum may become involved as well and somatic pain fibers from spinal nerves create the sensation of pain over the site of inflammation.[14]

Between 75% and 98% of patients with intestinal ischemia present with abdominal pain, and in the absence of such pain, unexplained distention and GI bleeding are the most frequent findings.[17] One study reports that the pain on presentation was most suggestive of renal disease in 5 of 22 patients.[32]

The absence of bowel sounds, although is occurs later on in the disease, is a frequent finding at the time of presentation in upwards of 50% of patients.[14] While the absence of sounds reflects the presence of a paralytic ileus, occasional tinkles may be heard, indicating air/fluid levels which are suggestive of more severe ileus.[14] Rarely, a loop of palpable distended bowel is discovered on exam as well.[32]

Bleeding is common in cases of acute, severe infarction but may not show up early on in at least 25% of cases when an

early diagnosis would mean a better prognosis.[1] For this reason, the absence of heme positive stools should never be used to rule out the presence of acute ischemic bowel.

Other signs and symptoms are less common but have proven valuable in forming a constellation of findings related to the diagnosis of intestinal ischemia. A list of findings as compiled by Pierce[28] are presented in Table III.

Table III - Finding on Initial Physical Examination[28]

	Incidence (percent)
Hypotension	15
Bradycardia	10
Tachycardia	31
Hypothermia	14
Fever	18
Signs of poor regional perfusion	
cool/cyanotic extremities	33
cyanosis of abdominal wall	21
Signs of saline depletion	35
signs of congestive heart failure	45
Abdominal tenderness	80
Abdominal guarding	45
Diminished or absent bowel sounds	60

Laboratory

There is no single discriminating laboratory finding reported in the literature although the patient with ischemic bowel often exhibits a range of abnormal blood and serum profiles. Elevated hematocrit secondary to massive plasma loss, and leukocytosis, are not uncommon findings. Elevated serum amylase, blood urea nitrogen, alkaline phosphatase, and

inorganic phosphate have been reported although the consistency of these findings has never been verified.[27] Other parameters examined in the past, and found to be non-specific, include blood glucose, peritoneal fluid cell counts and alkaline phosphatase, urine cell counts and protein, and stool guiac.[28]

In 1973 Brooks and Carey[24] proposed the utility of arterial blood gas measurements in diagnosing embolism of the SMA. Using the Siggard-Andersen[26] nomogram for calculating whole blood base excess(deficit), they found a significant difference between 7 patients with massive ischemia (mean base excess = -15, mean pH = 7.27) and 21 controls with other acute abdominal conditions (mean base excess = -.3, mean pH = 7.46).[24] They conducted further experiments in dogs and demonstrated that a base deficit appears within 3 to 6 hours after occlusion of the SMA and concluded that such a measurement would be valuable early on in the diagnosis of bowel ischemia.[24] Other experimenters have demonstrated that base deficit is also often a characteristic of intestinal gangrene secondary to other causes (volvulus, etc.) and that only significant occlusion of the SMA with extensive infarction is sufficient to produce a discriminant base deficit.[23] Many patients with lesser infarctions exhibit a normal acid/base profile.[23]

The specific etiology of the metabolic acidosis resulting from intestinal ischemia is uncertain, however, theories have

been advanced suggesting the involvement of intestinal endotoxins and vasodilating peptides.[24] Other theories emphasize the importance of tissue necrosis and anaerobic metabolism in creating the acid/base disturbance.[23,24]

Radiography

Plain Film

The plain film is the often first radiologic step in the evaluation of an unspecified abdominal condition. Several researchers feel that it should always be the first step when there is a suspicion of ischemic bowel.[6,17] Whether the specific technique used is the KUB or the 3-Way of the abdomen, a plain film may be diagnostic in about one out of five patients with acute intestinal ischemia.[1,6] One study cites positive plain film findings in 56 of 59 patients (95%).[33] The classic "thumbprint" is a common, and relatively specific, sign which is caused by hemorrhage or edema in the bowel wall creating radio-distinct mucosal hilocks.[1,17] Thumbprinting, however, may also be found in connection with other diseases.[8] The "rigid-loop" or "sentinel-loop" sign is defined by a single, narrowed loop of small bowel that remains unchanged in appearance over time or position of the body, and is another fairly specific finding of ischemia.[8,9]

The single most frequent finding of intestinal ischemia on the abdominal plain film is evidence of small bowel obstruction.[11] Gas, which accumulates in the lumen of the

small bowel as the disease progresses, often causes a visible distention, however, there is frequently a significant paucity of gas early after the onset of ischemia.[9] The phrase "gas-less abdomen" is used to describe this particular radiographic finding.[9] In the later stages of the disease, gas secondary to intestinal necrosis may also be visualized within the intestinal wall.[4] As gas continues to dissect the wall of the gut, it may eventually accumulate within the portal vein: a very ominous finding.[9] It is important to distinguish such gas from the benign condition of pneumatosis intestinalis in which cystic blebs of gas are seen within the wall of the gut.[8]

The other sign of obstruction is the presence of air/fluid levels within the small intestine. While air/fluid levels may be considered normal in the stomach, cecum, ascending colon, and terminal ileum, multiple air/fluid levels, especially in the small bowel, should be considered abnormal.[8] Despite the high frequency of intestinal obstruction in patients with ischemic bowel, it is certainly not a specific finding.

A plain film of the abdomen can, however, be very helpful in ruling out other conditions frequently included in the differential diagnosis with ischemic bowel such as a leaking, calcified abdominal aortic aneurysm, biliary or renal calculi, calcific pancreatitis, or a strangulating bowel obstruction.[6] For this reason, a plain film should always be the primary radiographic evaluation for the patient with

suspected intestinal ischemia. If the plain film does not offer an alternative explanation for the patient's abdominal distress, or if specific signs of ischemia are present, mesenteric angiography is the next required step.[6,17]

Angiography

Contrast visualization of the mesenteric vascular bed through abdominal angiography is probably the single most sensitive diagnostic tool used to detect intestinal ischemia, short of laparotomy. A study by Boley, et al. found that when the plain film was used to rule out abdominal disease other than ischemia in patients over age 50 with greater than 2 to 3 hours of sudden-onset abdominal pain, angiography was diagnostic in 33 of 35 (94%) patients with ischemic bowel.[17] In a similar study, Wittenberg, et al. were able to diagnose 27 out of 27.[6]

While both frontal and lateral projections of the SMA should be obtained, the lateral view is usually the most valuable.[2] Total occlusion within the first few centimeters of the SMA is generally diagnostic of a thrombotic lesion while emboli usually appear between three and eight centimeters from the origin.[1,4,6] The most common site for embolic obstruction is at the origin of the middle colic artery where contrast forms the shape of a "mercury meniscus" around the embolus.[1,4] Because thrombosis is generally a more proximal

lesion, it is likely that the entire small bowel distal to the ligament of Trietz will be affected.[4]

The inferior mesenteric artery, in contrast to the SMA, is more difficult to visualize and its occlusion is less diagnostically specific. In fact, in one study 40% of control patients with no abdominal pain demonstrated no opacification of the IMA on abdominal angiography.[6]

Angiography generally shows no occlusion in patients with non-occlusive disease although some patients do demonstrate a marked arterial narrowing, abnormal tapering of branches, or a non-uniform arterial spasm described by diminished and unequal flow.[6] Boley, et al. add that the impaired filling of intramural vessels is the forth reliable criteria for diagnosing non-occlusive disease by angiography.[17] Angiography is normally negative in patients with mesenteric venous thrombosis.[17]

In general, the procedure takes about 60 minutes to detect patients with occlusive arterial obstruction, and up to three hours for patients with non-occlusive disease.[1,6] Ongoing resuscitative measures can continue during this period of time. Several researchers, in stressing the importance of angiography as a diagnostic tool, assert that the results of the angiogram are important in the operating room while the angiographic catheter is also useful for administering vasodilators to the affected vessels.[6,17] Morbidity is low, as

well, they claim with no negative outcomes in 27 patients and 2 minor complications in 35 patients respectively.[6,17]

Upper GI and Barium Enema

Liquid contrast studies should be the final radiological technique employed in the patient with suspected ischemia of the small intestine, and can be done immediately after a negative plain film and a negative angiogram. They are useful for detecting conditions other than ischemic bowel and are performed last because the contrast interferes with the angiographic reading.[1,6] The barium enema is, however, useful for detecting colonic ischemia in which one may see the previously described "thumb-print".[2,17]

Other Radiological Techniques

Several other experimental methods of detecting ischemic bowel are reported. One, by Boley et al., uses the radioisotope ^{99m}Tc colloid-sulfur to label leukocytes which locate at the area of ischemia within two hours of onset and remain for approximately 24 hours.[17]

Although not a radiographic technique, laparoscopy has been used with some success in limited cases to view the bowels of patients in place of angiography. Intra-abdominal pressure is kept to a minimum (<20mmHg) to prevent intestinal circulatory compromise in these patients.[17]

SUBJECTS AND METHODS

To test the hypothesis that patients with ischemic bowel could be identified with a greater degree of sensitivity in the emergency room by means of their history and physical exam along with their laboratory and radiographic analyses, two groups of patients, one with ischemic bowel and one control group, were studied retrospectively. The following paragraphs describe the methodology of the selection of the case and control groups.

Case Subjects

The following criteria were used to select subjects with ischemic bowel for the case group through the Medical Records Department at Yale-New Haven Hospital. Each subject:

1) was admitted to YNHH <u>through the Emergency Service</u> between the years 1981 and 1987 (inclusive).

2) was 18 years of age or older.

3) was determined to have had <u>acute</u> ischemia of the small intestine at the time of presentation by either radiological, pathological (including autopsy), or surgical techniques.

4) had not experienced physical trauma to the abdomen prior to admission.

The 55 individual case charts were selected from the entire collection of over 250 charts between 1981 and 1987 bearing any of the following three standard diagnostic codings (ICD9-CM codes):

557.0 Intestinal Ischemia, Acute

557.1 Intestinal Ischemia, Chronic

557.9 Intestinal Ischemia, NEC

While only the final diagnosis of acute ischemia of the small intestine was permitted for each case, all of the charts from each of the three diagnostic categories were reviewed to prevent the omission of a valid case due to a clerical coding error.

To cross-check for selection bias a Pathology Department computerized listing of specimens of acute intestinal ischemia was compared with the list of charts requisitioned for study. Each unit number on the pathology department list corresponded to a requisitioned chart with only one omission (this turned out to be a patient with ischemic bowel who was mis-coded as gastrointestinal hemorrhage).

Control Subjects

The objective of the selection process of a control group was to compile a randomly selected population of patients who met the following criteria:

1) was admitted to YNHH through the Emergency Service between the years 1981 and 1987 (inclusive).

2) was 18 years of age or older.

3) complained of, or appeared clinically to have had, any moderate to severe abdominal condition presenting with, but not limited to abdominal pain, distention, diarrhea, nausea, vomiting, melena, obstruction, or obstipation.

3) did not have ischemia of the small intestine at any time from one year prior to, or during, the particular admission.

4) had not experienced physical trauma to the abdomen prior to admission.

The common occurrence of testing a patient's serum amylase was chosen as a sensitive marker to identify patients presenting with a moderate to severe abdominal condition. A randomly selected list of 161 patients who had had a serum amylase drawn in the Emergency Service and who were subsequently admitted to the hospital was generated by the Department of Laboratory Medicine. 34 of these charts met each of the control selection criteria #1-4 as listed above. To increase the size of the control group, additional control patients were then directly selected from the same diagnostic categories, and in the same ratios, as the randomly generated

group of heterogeneous abdominal diagnoses from the Department of Laboratory Medicine. Using this method, it was possible to generate control subjects who were matched in a 2:1 ratio to case subjects for both age (±4 years) and year of admission (±1 year).

Data Collection

An *Abdominal Pain Protocol* (Appendix A) sheet was completed for each case subject and control subject using data from the patient's chart. Only those data points were included which were felt to represent the status of the patient upon presentation to the Emergency Service. In instances where data appeared to conflict (ie. physical exam, presenting symptoms) priority was given to the ES sheet first, and then to the physicians' notes in the order in which they were written. Significant findings were entered on the data sheet by filling in the appropriate blank or circling the appropriate word or phrase. Reported negatives were represented by crossing out the corresponding word or phrase.

Data was then tabulated to produce descriptive breakdown reports of the demographics, diagnoses, and outcomes of the case and control control groups. Subsequently, the data was subjected to multiple grouping and regroupings for appropriate statistical analysis of the dependent and independent variables.

Statistical Methods

To test the hypothesis that a patient's history, symptoms, physical exam, laboratory and radiographic findings can be used to positively diagnose acute small bowel ischemia, simple chi-square (χ^2) correlations were examined between the case and control groups for categorical (including dichotomous) independent variables. For continuous variables, the data were subject to the standard T-test. Those single factors which were felt to be the best discriminators of ischemic bowel disease, either by statistical correlation or clinical impression, were then grouped in several different models for discriminant function analysis, a form of multi-linear regression.

RESULTS

Demographics of case/control

After a review of the data set for patients with ischemic bowel (cases), 49 of the original 55 charts were retained for analysis. A total of 94 control subjects were paired 2:1 to the case subjects (4 controls missing) for all of the following data analyses.

The mean age of the case subjects was 70, with ages ranging from 28 to 96 (S.D. = 17). The control subjects, who were matched for age±4 years had a mean age of 68 (S. D. = 16). Thirty-one (63%) of the case subjects were female and 18 (37%) were male. Similarly, 63 (67%) of the control subjects were female, and 31 (33%) were male. Both case and control groups were predominantly white (74% and 85%) respectively. And, while 86% of the ischemic patients were admitted to the surgery service, only 56% of the control patients were admitted to the same service. All in all, the case subjects had a very high case fatality rate per admission of 59% in contrast to the 6% rate for the controls.

Each case was categorized into one of 7 diagnostic groups which represent the various etiologies of ischemia (Table IV).

Table IV - Categories of Cases of Ischemic Bowel

Category	Count	Percent
SMA Embolus	6	12%
SMAThrombu	3	6%
Mes. Venous Thrombus	4	8%
NonOcclusive	4	8%
Focal/Segmental	16	33%
Massive NOS	13	27%
Vasculitis	1	2%
Undetermined	2	4%

Focal/segmental ischemia (38%), the most frequent category, contains a wide variety of ischemic insults, each limited to no more than an 18" length of involved bowel. Included are such common conditions as volvuli, adhesions, and incarcerated herniae severe enough to cause anoxia and necrosis of the bowel wall. The category "Massive NOS" is for those patients in whom massive bowel infarction was diagnosed, but no specific etiology was reported. The category "other" denotes ischemia of unreported extent or etiology.

Case fatality rates were then calculated for each of the various categories of ischemia and are presented in Table V.

Table V - Case Fatality Rates By Diagnosis

	dead	alive	Case Fatality Rate:
SMA Embolus	5	1	.83
SMAThrombus	3	0	1
MVT	2	2	.50
NonOcclusive	4	0	1
Focal/Segmental	4	12	.25
Massive NOS	9	4	.69
Vasculitis	0	1	0
Undetermined	2	0	1
Totals:	29	20	Mean: .59

Each of the 94 control patients was placed into one of 15 general diagnostic categories based upon their discharge diagnosis (Table VI).

Table VI - Diagnostic Categories of Matched Controls

Category	Count	Percent
Abdominal Pain	13	14%
Pancreatic Condition	8	9%
Appendicitis	6	6%
Ascites	1	1%
Cholecystitis	8	9%
Colon CA	4	4%
Diverticular Disease	7	7%
Colitis	2	2%
Ulcer	1	1%
Gastroenetritis	7	7%
GI Bleed	14	15%
Nephrolithiasis	4	4%
Sickle Cell	1	1%
SBO	15	16%
UTI	3	3%

Several of these categories contain a number of different, but related, specific diagnoses. For example, the category pancreatic condition happens to include pancreatic cancer, pancreatic pseudocyst, and acute pancreatitis. These generalized classifications were necessary to facilitate data handling in certain statistical calculations. As previously mentioned, the case fatality rate for all of the controls was 6%. The specific breakdown by category will not be presented here.

The number of hours between the onset of symptoms and presentation to the Emergency Service was tabulated for case

vs. control groups as well as the time between presentation and intervention. These time spans are reported in Table VII.

Table VII

t-tests on Time of Presentation and Time to Intervention
(x=all case/all control)

Y	nCase	nControl	xCase	xControl	*SD*Case	*SD*Control	*t*	Prob.(2-tail)
Onset to presentation	43	88	51.9	77.0	48.4	85.3	1.700	0.0752
Presentation to Intervention	45	12	42.6	73.5	88.3	90.1	1.072	0.2882
Total: Onset to Intervention	49	94	84.6	81.5	103.9	93.9	-0.184	0.8546

Predictive Diagnostic Statistics on Admission Variables

Those variables obtained on the admission of any patient which may, in some way, ultimately contribute to the correct diagnosis of the patient's disease are evaluated here for their importance as discriminators. t-Tests, analysis of variance (ANOVA), contingency table analysis (χ^2), and discriminant function analysis have been utilized to perform this investigation and the results of these tests are summarized below.

t-Tests

The results of standard t-tests (unpaired), performed on each of 37 continuous admission variables for all 49 cases and 94 controls, are reported in Table VIII .

Table VIII

t-tests on Admission Variables

(x=all case/all control)

Y	nCase	nControl	xCase	xControl	*SD*Case	*SD*Control	*t*	Prob.(2-tail)
age	49	94	69.6	67.5	16.7	16.2	-7.290	0.4673
Hrs. since last BM	21	23	38.6	33.1	27.9	42.6	-0.504	0.6168
Temp(F)	44	82	98.8	99.2	1.6	1.7	1.252	0.2128
Pulse	48	90	93.0	85.2	24.6	18.2	-2.127	0.0352*†
Systolic	49	90	127.7	134.7	37.8	26.9	1.268	0.2071
Diastolic	49	90	62.9	74.0	36.8	19.9	2.303	0.0228*†
Resp. Rate	43	73	24.3	19.6	6.6	5.8	-3.993	0.0001*†
Na	49	94	136.5	138.1	5.6	4.9	1.782	0.0769
K	48	94	4.3	3.9	1.0	0.6	-2.573	0.0067*
Cl	49	94	97.8	100.8	8.4	9.6	1.817	0.0713
HCO	48	94	21.5	26.3	6.8	8.7	3.322	0.0011*†
BUN	49	93	40.0	24.4	25.3	17.6	-4.298	0.0001*†
Creatinine	42	74	2.0	1.3	2.1	0.8	-2.334	0.0213*†
Glucose	49	88	194.7	151.3	121.2	78.5	-2.540	0.0122*†
HCT	48	94	41.7	38.2	7.8	9.3	-2.210	0.0287*†
WBC	49	93	17.4	13.3	12.1	13.3	-1.779	0.0774†
Segs	46	90	63.3	64.2	19.2	20.3	0.223	0.8236
Bands	45	89	18.8	10.0	19.6	12.5	-3.154	0.0020*†
Lymphs	43	85	9.3	13.5	6.6	8.2	2.853	0.0051*
Monos	39	75	5.7	6.0	3.4	3.7	0.380	0.7048
Eos	15	28	1.8	1.8	1.3	1.2	-0.113	0.9103
Arterial pH	28	18	7.3	7.4	0.1	0.1	1.424	0.1616
Co	28	18	28.7	30.5	8.4	5.5	0.820	0.4166
O	28	18	102.5	112.7	44.1	106.9	0.453	0.6531
%sat	25	15	93.9	95.3	8.4	2.1	0.636	0.5288
Calc. Bicarb.	25	15	16.7	20.5	7.1	4.8	1.829	0.0752†
Base Excess	28	18	-6.4	-2.7	8.8	5.2	1.576	0.1223
Amylase	39	79	116.2	106.3	98.1	295.7	-0.202	0.8401
Lipase	39	73	0.7	2.2	0.1	11.6	0.806	0.4219
Bilirubin	32	52	2.1	0.7	6.7	0.6	-1.452	0.1503
SGOT	37	50	117.6	31.2	363.2	25.7	-1.680	0.0967
Alkaline Phos.	36	52	64.6	54.9	118.7	46.0	-0.538	0.5918
LDH	17	8	621.5	383.6	348.3	123.6	-1.860	0.0758†
CPK	16	12	273.7	32.5	716.0	19.7	-1.161	0.2561

*p≤.05 (two-tailed)
†p≤.05 (one-tailed)

The two-tailed probabilities found significant at the p≤.05 are indicated by an asterisk (*) and those thought appropriate to be measured by a one-tailed test and found significant with a p≤.05 are indicated by a dagger (†).

Under the assumption that the patients with focal-segmental ischemia might have been less seriously ill than those with massive ischemia, t-values were recalculated which excluded those cases of focal/segmental disease (Table IX). Only those p values which reached a level of significance ($p \leq .05$) are reported. For those p-values that changed, the direction of change of the p value from the previous t-test is indicated in the last column. "↑" indicates an increased p-value (and hence a lower significance) "↓" indicates a decreased p-value from the previous test.

Table IX

Secondary t-tests on Admission Variables
(x=cases excluding focal/segmental disease/all control)

Y	nCase	nControl	xCase	xControl	*SD*Case	*SD*Control	*t*	Prob.(2-tail)	Δ
Pulse	32	90	94	85	27	18	-2	0.0366*†	↑
Diastolic	33	90	63	74	38	20	2	0.0353*†	↑
Resp. Rate	29	73	24	20	7	6	-4	0.0006*†	↑
Na	33	94	135	138	6	5	3	0.01*†	↓
K	32	94	4.2	3.9	1	1	-2	0.0163*	↑
Cl	33	94	96	101	10	10	2	0.0286*	↓
HCO_3	32	94	21	26	7	9	3	0.0014*†	↑
BUN	33	93	44	24	27	18	-5	0.0001*†	↔
Creatinine	27	74	2	1	3	1	-2	0.0252*†	↑
Glucose	33	88	212	151	140	79	-3	0.0033*†	↓
WBC	33	93	20	13	13	13	-2	0.0208*†	↓
Bands	31	89	20	10	19	13	-3	0.0016*†	↓
Lymphs	29	85	8	14	5	8	3	0.002*	↓
SGOT	27	50	153	31	422	26	-2	0.0446*	↓
LDH	13	8	651	384	384	124	-2	0.0735†	↓

*p≤.05 (two-tailed)
†p≤.05 (one-tailed)

While several p values increased in significance (glucose, WBC, bands) most remained essentially unchanged. An analysis

of variance (ANOVA) was then performed between the various case categories (using the same dependent variables) in order to determine whether or not a significant difference existed between any of the diagnostic groups of ischemia. Although some of the p values approached or reached significance, the numbers within each group were relatively small and the results have not been included in this study.

To examine the effect of non-parametric distribution in a few of the continuous variables, t-tests were then re-run for those variables in which it was thought that a small number of unusually high values were either spurious or caused by another specific disease process unrelated to ischemic bowel (Table X).

For the same reason, a t-test was re-run on the variable amylase in which patients with known pancreatitis were removed from either the case or control group (Table XI).

Table X

t-tests re-run on Bili/SGOT/Alk.Phos./CPK
(x=case/control - excluding excessively high values)

Y	nCase	nControl	xCase	xControl	*SD*Case	*SD*Control	*t*	Prob.(2-tail)
Bilirubin	30	52	0.811	0.767	0.475	0.623	-0.331	.7418
SGOT	34	50	32	31	24.122	25.733	-0.136	.892
Alkaline Phos.	35	52	45.2	54.9	21.9	46.043	1.16	.2495
CPK	15	12	96.6	32.5	108.2	19.774	-2.019	.0543

Table XI

t-test re-run on Amylase/Lipase

(x=case/control - excluding pancreatitis)

Y	nCase	nControl	xCase	xControl	*SD*Case	*SD*Control	*t*	Prob.(1-tail)
Amylase	39	71	116	60	98	27	-4.496	.00005
Lipase	39	67	0.78	1.9	0.57	11.8	0.64	.5233

Predictive Outcome Statistics on Admission Variables

Once again using the standard t-test, the life/death outcome of our set of case patients with ischemic bowel is compared using the same assortment of admission variables. Three new categories have been added: the time from onset of symptoms to presentation, the time from presentation to surgical intervention (if any), and the total time from onset of symptoms to intervention. Table XII summarizes this analysis.

Table XII

t-tests on Admission Variables - alive vs. dead

(x=cases discharged alive/died during admission)

Y	nAlive	nDead	xAlive	xDead	*SD*Alive	*SD*Dead	*t*	Prob.(2-tail)
age	20	29	64.9	72.9	17.5	15.6	1.663	0.103
Hrs. since last BM	12	9	36.6	41.3	29.3	27.4	0.37	0.7151
Temp(F)	18	26	99.1	98.7	1.3	1.8	-0.813	0.4207
Pulse	20	28	86.3	97.9	22.2	25.4	1.643	0.1071
Systolic	20	29	132.6	124.4	38.7	37.6	-0.74	0.4632
Diastolic	20	29	71.6	56.9	33.6	38.2	-1.38	0.1741
Resp. Rate	18	25	22.3	25.7	5.5	7.1	1.67	0.1026
Na	20	29	139.0	134.7	4.0	5.9	-2.789	0.0074*
K	20	28	4.1	4.5	0.6	1.3	0.968	0.338
Cl	20	29	101.4	95.3	5.6	9.2	-2.633	0.0114*
HCO	19	29	23.2	20.4	5.8	7.3	-1.413	0.1645
BUN	20	29	26.3	49.5	15.4	26.6	3.502	0.001*†
Creatinine	18	24	1.3	2.5	0.4	2.7	1.844	0.0726†
Glucose	20	29	153.3	223.3	47.1	147.1	2.051	0.0459*†
HCT	20	28	43.5	40.3	6.3	8.6	-1.379	0.1745
WBC	20	29	13.5	20.1	6.1	14.4	1.92	0.061†
Segs	19	27	67.6	60.4	16.7	20.6	-1.262	0.2136
Bands	18	27	15.8	20.7	20.4	19.1	0.815	0.4194
Lymphs	18	25	11.4	7.9	8.4	4.4	-1.769	0.0843
Monos	19	20	6.1	5.4	3.5	3.4	-0.634	0.53
Eos	7	8	2.4	1.3	1.6	0.7	-1.658	0.1212
Arterial pH	8	20	7.3	7.3	0.1	0.1	-0.227	0.8226
Co	8	20	28	29	5.0	9.5	0.279	0.7821
O	8	20	108.1	100.2	27.6	49.7	-0.418	0.6797
%sat	8	17	96.9	92.4	2.2	9.8	-1.26	0.2204
Calc. Bicarb.	8	17	18.4	15.9	6.5	7.4	-0.81	0.4263
Base Excess	8	20	-5.3	-6.8	8.7	9.1	-0.391	0.699
Amylase	19	20	91.7	139.4	75.4	112.7	1.541	0.1317
Lipase	19	20	0.6	0.8	0.4	0.6	0.907	0.3705
Bilirubin	14	18	0.7	3.2	0.3	8.9	1.044	0.3048
SGOT	17	20	26.4	195.1	16.3	485.8	1.428	0.1622
Alkaline Phos.	16	20	79.1	53.0	178.0	25.2	-0.651	0.5197
LDH	7	10	470.8	727.1	201.2	398.3	1.5	0.1401
CPK	5	11	152.6	328.8	177.0	863.5	0.444	0.6639
Hours since onset	19	24	28.5	70.4	27.4	53.6	3.087	0.0036*†
Hours to intervention	20	25	26.1	55.7	21.6	116.3	1.1	0.2686
Onset to intervention	19	21	54	136.0	36.0	138.0	3.0	0.0158*†

*p≤.05 (two-tailed)
†p≤.05 (one-tailed)

Chi Square (χ^2) Analysis

Standard contingency tables were constructed for each of the categorical predictive variables for the cases vs. controls. χ^2 analysis was then performed to find those variables whose values differed significantly between the two groups. The results of these analysis are presented in Table XIII. Those contingency tables which generated a p value $\leq$ .05 are marked with an asterisk (*).

Several contingency tables were then recreated for subsets of the entire case/control population to eliminate those patients from the analysis whose particular variable values fell significantly outside the normal distribution for reasons that were either clinically apparent or not reasonably related to ischemic bowel.

Table XIII

χ^2-tests on Admission Variables

(x=case/control)

Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity correction)	P value
Demographic (patients matched for age and year of admission)						
Sex						
male	18	31				
female	31	63	0.2	.6533	.07	.7922
Race						
white	37	79				
black	5	10				
Hispanic	1	1				
other	0	1	1	.8543		
Admitting service						
medicine	7	41				
surgery	42	52	13	.0004*	11	.0007*
Patient History						
Onset						
sudden	19	28				
gradual	1	22	10	.0017*	8	.0043*
Onset intensity						
mild	1	12				
moderate	6	30				
severe	20	15	18	.0002*		
Onset site						
LLQ	1	10				
LUQ	2	3				
RUQ	2	8				
RLQ	3	8				
umbilical	2	2				
generalized	20	21				
chest	1	4				
epigastric	7	7				
other	3	2				
none	8	29	28	.1004		

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Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity	P value correction)
Site Now						
LLQ	0	9				
LUQ	0	2				
RUQ	1	10				
RLQ	3	9				
umbilical	0	2				
generalized	18	16				
chest	0	1				
epigastric	2	4				
other	1	1				
none	1	0	19	.0285*		
Intensity now						
mild	1	6				
moderate	1	28				
severe	19	18	19	.0001*		
Quality of pain						
crampy	13	22				
sharp	0	11	6	.017*	4	.0452*
Type of pain						
intermittent	1	20				
constant	11	3	20	.0001*	17	.0001*
Associated pain						
flank	1	8				
shoulder	0	3				
thigh	1	0				
chest	3	8	5	.1459		
Fever (history)						
yes	3	15				
no	13	27	2	.2121	1	.352
Chills						
yes	2	11				
no	13	27	1	.234	1	.4033
Sweats						
yes	1	4				
no	2	5	0.1	.7353	0.1	.7353
Headaches						
yes	1	0				
no	1	3	2	.1709	0.05	.8195
Lightheadedness						
yes	1	9				
no	0	2	0.2	.6404	1	.3502
Anorexia						
yes	9	14				
no	2	7	1	.3652	0.2	.6231
Nausea						
yes	30	39				
no	12	19	0.2	.655	0.05	.8198

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Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity	P value correction)
Vomiting						
yes	31	46				
no	13	22	0.1	.7542	0.01	.9169
Bilious vomiting						
yes	6	2				
no	0	1	2	.1336	0.1	.7077
Bloody vomit						
yes	2	2				
no	9	9	0	1	0.3	.5804
Coffee ground						
yes	8	3				
no	2	1	0.04	.8368	0.3	.6066
Diarrhea						
yes	13	21				
no	6	12	0.1	.7269	0.002	.9629
Bloody stool						
yes	4	11				
no	1	6	0.4	.5186	0.01	.9209
Black stool						
yes	4	5				
no	0	4	3	.1091	1	.3414
Past similar episode						
yes	10	40				
no	8	28	0.06	.8027	0.0004	.985
Previous abdominal surgery						
yes	32	53				
no	9	17	0.08	.7793	0.002	.9616
CHF (history)						
yes	14	12				
no	1	5	3	.1	1	.2336
A-Fib (history)						
yes	12	3				
no	3	1	0.05	.8275	0.2	.6368
Physical Exam						
Motion						
still	2	2				
writhing	6	0	4	.0528*	1	.2586
Dehydration signs						
yes	14	10				
no	2	4	1	.2723	0.4	.5219
Abdominal distention						
yes	30	23				
no	3	4	0.5	.492	0.08	.7772

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Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity correction)	P value
Bowel sounds						
present	26	84				
absent	20	4	31	.0001*	29	.0001*
Tenderness						
RUQ	4	14				
LUQ	0	1				
RLQ	5	12				
LLQ	2	12				
general	29	13				
none	1	33	43	.0001*		
Rebound						
yes	7	5				
no	24	57	4	.049*	3	.1009
Guarding						
yes	11	7				
no	24	53	6	.0177*	4	.0358*
Rigidity						
yes	5	0				
no	21	51	10	.0012*	8	.006*
Murphy's						
yes	1	4				
no	18	48	0.1	.7232	0.0	3.8652
Psoas						
yes	0	1				
no	17	37	0.5	.4997	0.2	.6767
Pain out of proportion						
yes	2	0				
no	0	1	3	.0833	0.2	.665
RUQ mass (liver)						
yes	4	9				
no	20	55	0.09	.7591	0.0009	.9755
RLQ mass						
yes	3	4				
no	21	47	0.04	.5178	0.0	5.8249
LLQ mass						
yes	0	1				
no	24	49	0.5	.4855	0.1	.7055
Heme in stool						
yes	20	32				
no	22	55	1	.2396	1	.3249
Rectal tenderness						
yes	2	0				
no	0	3	5	.0253*	2	.1921

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Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity correction)	P value (w/continuity correction)
Laboratory						
Urine WBC's						
0-1	17	28				
2-5	11	26				
6-10	5	7				
11-20	2	5				
20+	4	8	1	.9135		
Urine RBC's						
0-1	22	50				
2-5	6	11				
6-10	3	4				
11-20	6	3				
20+	3	4	5	.2974		
Normal PT/PTT						
yes	31	54				
no	11	14	0.5	.4958	0.2	.6549
EKG						
A-Fib						
yes	9	4				
no	20	35	5	.0312*	3	.0653
Radiography						
A/F levels						
yes	14	10				
no	5	40	17	.0001*	15	.0001*
SB distention						
yes	30	17				
no	4	39	28	.0001*	26	.0001*
Free air						
yes	4	3				
no	2	3	0.3	.5582	0	1

Note: While many other variables were collected on the protocol sheet, they did not generate a response sufficient to calculate a χ^2 value. They are not reported above.

Table XIV

Secondary χ^2-tests on Admission Variables

(x=case/control ***excluding patients with frank GI bleeding***)

Y	nCase	nControl	χ^2	P value	χ^2 (w/continuity correction)	P value (w/continuity correction)
Guiac positive stool						
yes	20	20				
no	22	53	5	.0284	4	.0467*†
Onset intensity						
mild	1	10				
moderate	6	28				
severe	20	15	18	.0004†*		
Onset site						
LLQ	1	10				
LUQ	2	3				
RUQ	2	8				
RLQ	3	8				
umbilical	2	2				
generalized	17	20				
chest	1	4				
epigastric	7	6				
other	3	2				
none	8	20	28	.1129		
Site Now						
LLQ	0	8				
LUQ	0	2				
RUQ	1	10				
RLQ	3	9				
umbilical	0	2				
generalized	18	12				
chest	0	1				
epigastric	2	4				
other	1	1				
none	1	0	21	.0119†*		
Intensity now						
mild	1	3				
moderate	1	26				
severe	19	18	17	.0002†*		

Other Radiograph Results

Plain film results of radiography are presented in the contingency table analysis above. Other radiographic procedures which were used on both case and control patients

include barium studies, ultrasound, CT scan, and abdominal angiography. The actual numbers of these studies are too low to perform a formal statistical analysis, however descriptive results will be reported.

Barium enemas were read as normal in 3 of the 4 case patients and 7 of the 13 of the controls to whom they were given. Positive results included diverticulitis in 5, appendicitis in 1 and polyposis in 1. Upper GI series, administered in two of the controls were unremarkable.

One case of mesenteric venous thrombosis was diagnosed by abdominal ultrasound and the finding of ascites was present on another. Three case patients had normal ultrasounds. In the control group, 11 of the 13 abdominal ultrasounds administered were significant for either gallbladder disease or nephrolithiasis. The remaining two were normal.

Intravenous pyelography (IVP) diagnosed a case of renal stones in one of the two control patients to whom it was given. No patient with ischemic bowel received an IVP.

A HIDA scan was normal one case patient, and diagnostic for gallstones in four controls.

Mesenteric angiography was performed on 6 of 49 case patients and was diagnostic in all. 5 of the 6 had obstruction of the SMA, and one had a twisted ileocolic

volvulus. One control patient had angiography which located a bleeding vessel in the colon.

CT scan was performed on 2 cases and no controls. In one of the two cases it was diagnostic for mesenteric venous thrombosis, in the other it demonstrated only dilated loops of small bowel.

Additional Results

The incidence of patients taking narcotic pain killers, cardiac glycosides, and anticoagulants was recorded. Simple χ^2 statistics were generated for each group of medication. 15 of 49 cases (31%) took some form of digitalis prior to admission in contrast to 16 of 94 controls (17% - p=.0612).

Anticoagulants were taken by only a small number of patients from either group, 4 of 49 cases (8%) and 1 of 93 controls(1% - p=.0283). Narcotic pain killers were taken by 4 case and 3 control patients respectively (p=.191).

The case fatality rates associated with each of these three drug classes for patients with ischemic bowel are: narcotics 50% (2 of 4), anticoagulants 50% (2 of 4), and glycosides 66% (10 of 15).

Discriminant Function Analysis

Discriminant Analysis[42], a specialized form of multilinear regression, was used to evaluate various models of continuous

admission variables for their ability to predict the presence or absence of ischemic bowel disease. Different models were created from certain variables based either on the variable's univariate F and p values or on clinical/pathophysiological suspicion of the variable's ability to predict disease. Additional variables were then added, or deleted, one at a time based upon their individual contributions to the model's predictive value and the model was then reevaluated using Wilks's Lambda as the multivariate test statistic to measure the residual discrimination. Each variable was examined for its adherence to the parametric assumptions required for a valid discriminant analysis (normal distribution and equal covariance matricies[43]) and those cases which failed these assumptions were either transformed or eliminated from the model. The number of variables in the model was limited to five or fewer and a model was selected which had a combination of the highest predictive value and least Wilks's Lambda. The variables used in the final model were:

1 - ln(Amylase)
2 - ln(HCO_3)
3 - Glucose

The specific computation of the model along with the canonical correlations are included in Appendix B. The equation, based on the canonical coefficients, is derived from the factor scores of the means of the 2 groups (case/control) where the absolute value of the distance

between the mean factor score (d_2) and the individual factor score of the variable (d_1). The probability of being in the case group can then be expressed as follows:

$$\text{Probability of being in Group 1} = \frac{\exp(-\frac{1}{2}(d_1)^2)}{\exp(-\frac{1}{2}(d_1)^2)+\exp(-\frac{1}{2}(d_2)^2)}$$

$$\text{where } \exp(-\tfrac{1}{2}(X)^2) \approx \text{normal density function}$$

To build an specific equation based on this model, the general form $\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \ldots = F$ is used where β is the canonical coefficient of x_n, the value of the particular variable.

Our discriminant equation then becomes:

$$.736(\ln(\text{amylase}))-.417(\ln(HCO_3))+.461(\text{glucose})=F$$

μ_*, is then calculated from the factor loading means, μ_1 and $\mu_.$, by the equation $\mu_* = \frac{(\mu_1+\mu_2)}{2}$ and it follows that:

if $F-\mu_*>0$ then the equation predicts a **control**

if $F-\mu_*>0$ then the equation predicts a **case**

For this particular model, the computer predicted the entire data set as follows:

TABLE OF GROUP (ROWS) BY PREDICT (COLUMNS)

FREQUENCIES

	.	1	2	TOTAL	
1	11	27	13	49	1=CASE
2	19	17	50	86	2=CONTROL
TOTAL	30	41	64	135	

Positive predictive value = 71%

Negative predictive value = 75%

While various models that were analyzed generated higher positive and negative predictive values, they contained more variables (6+) and caused the equation to become increasingly complex, adding very little to the final outcome.

DISCUSSION

Discussion of Demographics and case/control selection

While the age range of subjects in this study (mean = 70, S.D. = 17) is not unlike that of most reports of ischemic bowel, the sex distribution (67% female) is in contrast to most reports which find the incidence of ischemic bowel to be somewhat higher in males.[17] The proportions of patients placed in a specific diagnostic category, save for non-occlusive disease, demonstrated relative frequencies of ischemic disorders similar to those reported in most studies for a sample of this size[27,29]. The groups "massive NOS" and "other" were unfortunately patients who were unclassifiable by the information contained in their charts. Frequently, these were elderly patients who were found to have inoperable massive infarction at laparotomy and did not undergo autopsy; thus, no pathological specimen was ever obtained. It is reasonable that many of these same patients might in actuality have had non-occlusive disease, as many of them had clinical histories similar to those reported in the literature. It should be remembered that most other studies do not limit their patient populations to emergency admissions, and thus see the onset of ischemia in hospitalized patients which is often of the non-occlusive type, precipitated by surgery or medication.

Case fatality rates within the various diagnostic categories are also in line with the work of other studies.[2,13,17]

As might be expected, the ischemic patients with embolic, thrombotic, non-occlusive, and other massive ischemic disease had the highest case fatality, while the focal/segmental patients had the best survival rate (Table V). Of interest is the observation that although the focal/segmental group showed similar demographic characteristics with respect to age, race, and sex, all 16 (100%) were admitted to the surgical service in contrast to the remainder of severely ischemic patients of which 7 (21%) were admitted to medicine. Perhaps this is an indication that the overt signs of bowel obstruction often related to focal/segmental disease are more readily appreciated than the complex clinical picture of the critically ill patient with massive bowel infarction.

The control patients, who were also categorized into diagnostic categories to facilitate analysis, demonstrated a typical cross section of pathologic conditions commonly found in patients admitted to the hospital from the Emergency Service for abdominal and related complaints (Table VI). While specific statistics are not readily available to substantiate this claim, the methodology of random selection more than likely produced an acceptable control group of patients with abdominal complaints presenting to the Emergency Service and subsequently admitted to the hospital.

The most common abdominal diagnoses included small bowel obstruction (SBO), abdominal pain of uncertain etiology, and gastrointestinal hemorrhage. The category of small bowel

obstruction was made up chiefly by those patients with adhesions, volvuli, and herniae that were not sufficient to cause ischemia or necrosis. Patients with GI hemorrhage generally did not have abdominal pain, and presented with a chief complaint related to bleeding, regardless of amount or origin, in the stool. Unlike the case subjects, control subjects were less likely to be admitted to the surgical service; only 56% compared with 86% for patients with ischemia. Furthermore, the substantially lower case fatality rate for the controls (6%) probably indicates that, as a whole, control patients had conditions that were less acutely life-threatening.

There was no significant difference ($p=.0752$) found in the speed of presentation by either group to the Emergency Service, although the mean time for controls to present was about 24 hours longer than that for cases (Table XII). The average of total time between onset of symptoms and intervention (if any) in both cases was essentially the same (Table XII) at just over 80 hours. For many conditions this would not be an inappropriate period of time, however, with the understanding that irreversible ischemic changes take place in bowel that has been hypoperfused for greater than 6 hours[2], an average time to intervention of over 3 days is simply too long.

Discussion of t-test analysis of Admission Variables

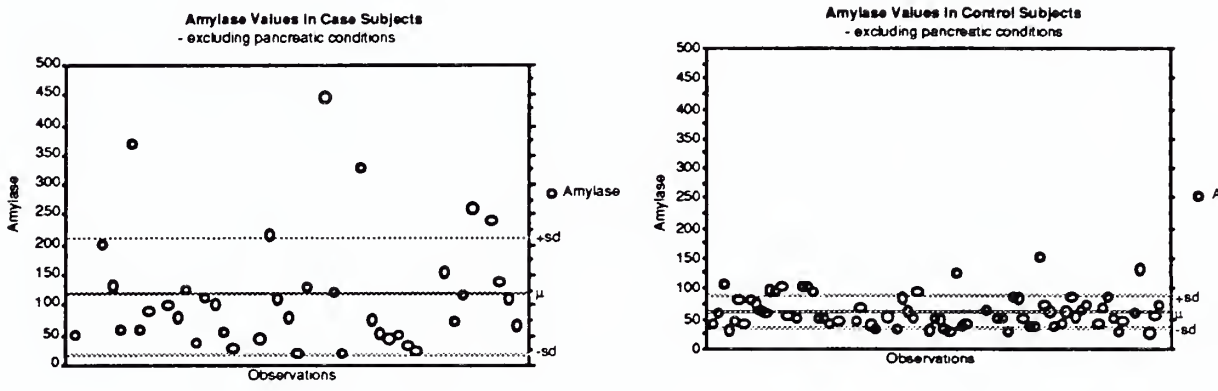
Of all the variables analyzed by standard t-tests (Tables VII, VIII, IX, X, XI) there are several that appear by their probabilities to separate patients with ischemic bowel from the control patients. In Table VII the variables pulse, diastolic blood pressure, respiration rate, potassium, bicarbonate, BUN, creatinine, glucose, hematocrit, white count, bands, base excess, and LDH all showed some degree of significance, although certainly less for some than others. Physiologically, it is not difficult to appreciate the combination of a rapid pulse and a lowered diastolic blood pressure accompanied by an elevated blood glucose, leukocytosis and metabolic acidosis in those patients presenting in early or frank sepsis secondary to an ischemic insult of the gut. While the means may be significantly different for these parameters, the narrow margins which separate the means of the pulse, blood pressure, and respiration rate, in conjunction with their wide standard deviations would make them poor specific predictors of ischemic bowel. The elevated BUN, creatinine, and hematocrit are likely indicative of dehydration with the concomitant hypovolemia of peritoneal "third-spacing". Again, narrow margins of difference and wide standard deviations eliminate all but the BUN as possible predictors of disease. Disappointingly, the arterial base excess, as calculated from the

Siggard-Andersen[26] nomograms (Appendix C) demonstrated a one-tailed p value of only .061 in this study population. As mentioned previously, this is a value which has received much discussion in the literature as a discriminator of ischemic disease[23,24].

Amylase, as an enzyme present in normal bowel, has been noted by other researchers to be somewhat elevated in patients with ischemic bowel[27] although its consistency has never been verified. In fact, the mean amylase in the case patients in this study is elevated at a level of 116.2, although it does not have a p value of significance when compared with the controls as a whole. If, however, the 8 patients with pancreatic conditions are removed from the control group and the t-test is rerun, amylase is found to be significantly higher in patients with ischemic bowel (p=.00005), although the standard deviation (98) is fairly wide (Table XI). On the other hand, lipase, an enzyme specific to the pancreas, shows no significant difference between groups.

The wide standard deviation, however, may seriously inhibit amylase as a discriminator, as can be appreciated from a scatter plot of the amylase values draw from the same data (Figure 3).

Figure 3



Several other continuous variables had means and standard deviations that were skewed by a very small number of markedly elevated values (ie. bilirubin, SGOT, alkaline phosphatase, and CPK). These values were felt to be a result of underlying conditions (ie. hepatic, renal, etc.) and unrelated to the diagnosis of ischemia. When the patients with these values were eliminated from the data analysis, only CPK approached statistical significance (Table X).

Discussion of t-tests on Outcome Variables

One would predict that those patients with ischemic bowel who died from this condition might have presented to the Emergency Service with a more impressive physical exam and distinctive laboratory values indicative of their profound illness. For this particular patient population, this does not seem to be the case. Although the modestly significant differences found in the WBC, BUN, creatinine, and glucose

and probably indicate a more advanced degree of sepsis and dehydration, other physiological parameters, such as pulse, blood pressure, hematocrit and even blood gas analysis, did not appear to be different between those patients who lived and those who did not (Table XII).

A particularly significant variable, which should come as no surprise, is the total time from onset of symptoms to intervention. Not only do the patients who live present much earlier on than those who do not, but they received earlier treatment and had a better chance of survival ($p=.0158$). Although there is a great variation in the time it takes the physician to intervene, on the average, intervention took only half the amount of time for patients who lived. The standard deviation for those who died, however, is so wide in this group of patients that the actual difference becomes insignificant ($p=.2686$). These data reconfirm the need for appropriate diagnostic tests and the ability to raise the clinician's suspicion in the face of intestinal ischemia so that patients can be identified and treated in the least amount of time possible.

Discussion of Contingency Table (χ^2) Analysis

Before proceeding with a discussion of the specific results, it is important to make mention of the specific collection methodology of this retrospective study in so far as yes/no responses are concerned. Any yes/no study variable

found to be true in a patients chart at the time of admission was recorded as a 'yes' value. Any variable specifically denied by the patient or physician was reported as a 'no'. Variables were not recorded if no mention was made of them, ie. if no pertinent negative was recorded. Therefore, if a patient reported 'nausea' but neither confirmed or denied vomiting (as recorded in the chart) *neither 'yes' nor 'no' was recorded on the study protocol form*. This unfortunately, but substantially, reduces the number of data points available for many of the yes/no questions, and frequently a p value will be significant when in fact the actual sample size was much to small to evaluate reliably. To demonstrate this point, the responses to the variable 'motion' (to which the responses are 'still' or 'writhing') are examined.

Observed Frequency Table for Motion

	still	writhing	Totals:
control	2	0	2
case	2	6	8
Totals:	4	6	10

Here $\chi_2 = 4$ (p=.05), but clearly with only 10 of 145 patients responding we would be hard pressed to guess whether the other 135 were still, writhing, or doing something completely different. The continuity correction (whose discussion is beyond the scope of this paper) may be used when sample sizes are small; in this case $\chi_2 = 1$ (p=.26) with

the continuity correction. Both are reported, but for many variables, neither is believed to be a reliable representation of the data as it might appear had a study been done prospectively. Nevertheless, there is a great deal of information to be gained from some of the contingency table analysis; and while not all of it may be 'statistically significant', the observations made (and in some cases the apparent lack of observations made in the clinical setting) can be very revealing.

The common presentation(s) of ischemic bowel were examined as demonstrated by the data collected in this study. Although patients with ischemic bowel were predominantly white and female, so were their control counterparts; perhaps a function of the age of both groups. Patients most commonly reported sudden onset (95%), severe (74%), and generalized (49%) abdominal pain which, upon presentation to the emergency service, was still severe (90%), and generalized (69%). In 11 of 12 cases the pain was constant and in 13 of 13 cases the pain was described as crampy and not sharp. Associated pain was uncommon, as was a report of fever, chills, sweats, lightheadedness, or headaches. GI symptoms such as anorexia (9 of 11), nausea (30 of 42), vomiting (31 of 44), and diarrhea (13 of 19) were all commonly reported but not with frequencies different from that of the control group. 55% had had a past similar episode, and most (78%) had had prior abdominal surgery. Again, these are non-specific

indicators and were found in similar proportions of the controls.

A history of CHF, while reported twice as frequently in the case group, may simply indicate that the physicians had performed a more complete history on these sicker patients; it nevertheless failed to generate a significant p value. A positive history of A-fib was reported far more frequently in those patients with ischemic bowel (25% of 49 patients) than in the control group (3% of 96 patients). The presence of A-fib on EKG was more frequent in the case group as well (9 of 29 compared to 4 of 39: p=.03).

Physical signs of dehydration, such as poor skin turgor and dry membranes were also more commonly reported (15 cases vs. 10 controls) in patients with ischemia but the lack of reporting of good hydration (a significant negative) makes the calculation of precise statistics difficult here as well.

Portions of the abdominal exam were significant in that only 4 of 88 controls reporting had no bowel sounds whereas 20 of 46 cases reporting (43%) had absent sounds on auscultation. This, however, only makes the absence of such sounds an ominous finding; the presence of bowel sounds is in no confirms or denies the presence of disease. Ischemic patients were also more likely to have generalized tenderness on exam whereas their counterparts may have had tenderness locally, generally, or none at all. Neither peritoneal signs

nor the presence or absence of masses were in any way specific for either the presence or absence of ischemia.

Heme positive stool, while present in 20 of 42 cases was also present in 32 of 87 controls (p=.239), although when the frank GI bleeders are removed from the analysis the p value drops to .028. Clearly, a positive hemocult without gross blood should raise one's suspicion of ischemic bowel in the presence of other findings. Heme negative stool, however, should never rule out the possibility of ischemic disease.

The secondary recalculation of χ^2 statistics without GI bleeders (Table XIV) was also done to reevaluate the significance of the pattern of pain on presentation. The basis for this investigation was the fact that over 90% of the GI bleeders presented without pain but with frank lower GI bleeding that was felt unlikely to be confused with a presentation of ischemic bowel. Although the p values fell slightly for severe, generalized pain, they maintained significance in differentiating the case group.

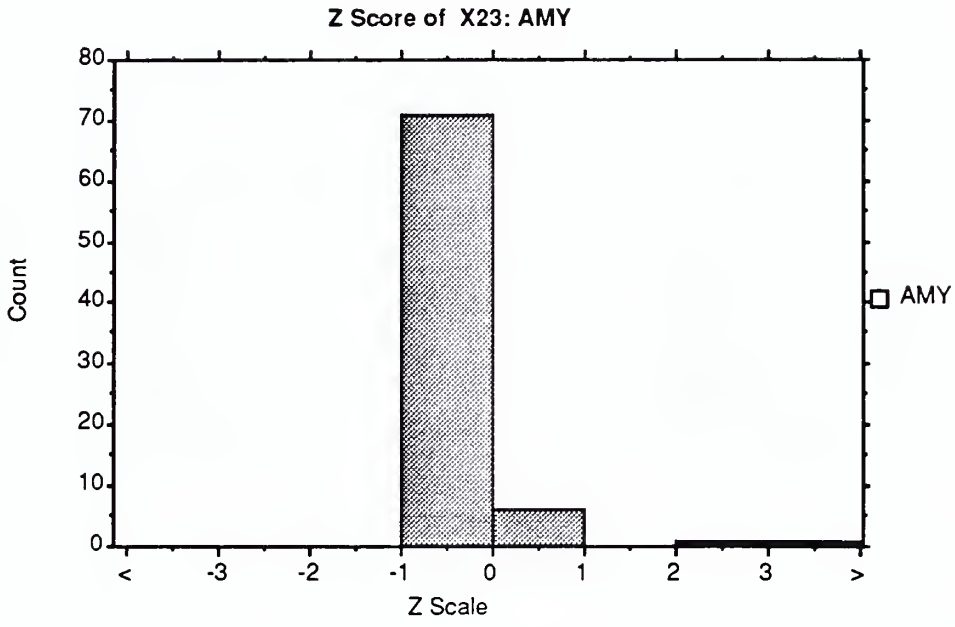
Plain film radiographs were analyzed for signs of ischemia and signs of bowel obstruction in both groups. While ischemic signs such as gas in the portal system, thickened rigid loops and frank perforation were not the rule in ischemic patients (although highly predictive when present), all but 4 of 39 patients had air/fluid levels and at least one loop of dilated small bowel. In contrast, only 22 of 61 controls had

this sign (those with SBO); and while not necessarily specific, it should raise a strong suspicion in a patient who may have other symptoms of ischemia.

Discussion of Discriminant Function Analysis

Discriminant analysis, introduced by R. A. Fisher[42] in 1936 is a specialized form of multilinear regression used to classify persons or things. By calculating a series of weighting vectors on two or more mutually exclusive groups one can later use these vectors to classify a newly observed person or thing into one of the groups. As with any statistical method, however, there are certain caveats to calculating and using a discriminant function. Perhaps the most constraining feature of discriminate analysis, as it pertains to the study at hand, is that each of the variables used must have a multivariate normal distribution.[42,43,44] Several, if not many, of the continuous variables used in this study do not precisely fit this normal distribution. For example, consider the values of amylase in the control group which are plotted in Figure 4.

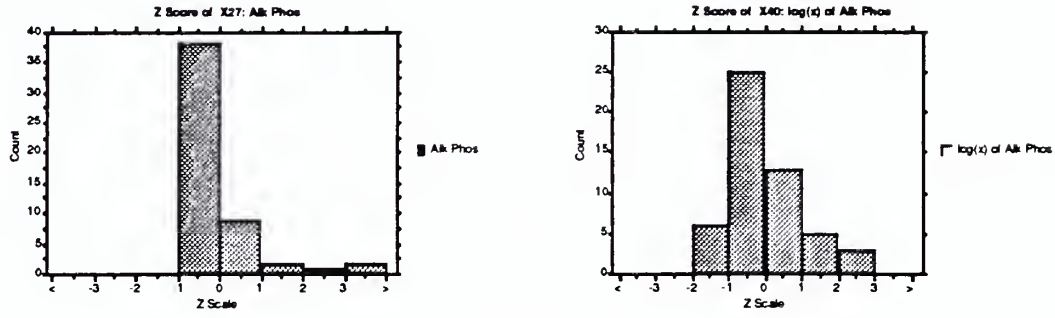
Figure 4



Bimodal distribution of this nature is not infrequently seen within the context of laboratory values. The underlying reasons for this phenomena, which are as numerous as there are variables, include sampling and measurement errors or actual bimodal populations. In the case of amylase, the small hump of elevated values likely represents those individuals with pancreatic conditions. To use this data in a parametric analysis, such as discriminant analysis, one must remove these cases from the study population, with the caveat that the study is no longer valid for patients with pancreatitis.

Another form of non-normal distribution is the skewing of data as can be seen in Figure 5.

Figure 5



The specific reasons for this condition are multi-fold, but one solution is to recode the data to equal the $\log_e$ of the original variable. If this transformation is able to restore normal distribution to the data, the variable then becomes useful in the discriminant analysis. In our example, the graph of ln(alkaline Phosphatase) demonstrates a partial restoration to normal distribution.

In the particular discriminant function presented in the results section, it was necessary to transform each of the variables logarithmically before entering them into the model. The effect of such a transformation is two-fold: it increases the validity of the model by conforming the variables to meet parametric standards, but at the same time it decreases the precision with which the model is able to discriminate between groups.

This model is in no way intended to represent the best possible model, even for this set of data. An automated

stepwise procedure was intentionally not utilized in the generation of this particular discriminant function for several reasons. The primary reason is that any stepwise procedure will give a "good fit" model, however, in a data set of this size having large standard deviations within the variables, such a technique would ignore the importance that physiological considerations must play in assessing the "reasonableness" of a particular model.

The predictive value of the model generated by this data is limited to this data set. Probability would dictate that for another data set the predictive value would be lower. Models such as these require testing and re-testing along with altering the combination of variables as more data is produced. However, the significance of this model lies not in its ability to confirm or deny the suspicions of the clinician when faced with the diagnosis of a case of ischemic bowel. The model is important because it implies that there are alterations in certain physiological and biochemical parameters in a patient with ischemia, whether or not these parameters have been included in this particular model. A prospective study of a larger scale might very well be able to define a model with a greater predictive value if, in fact, such a model exists.

Additionally, a prospective study could collect data on categorical variables that would allow their inclusion into a logistic regression along with of the continuous variables

studied here. Such a procedure was not performed here because of the categorical responses did not generate enough data points of their own. Combining both categorical and continuous variables would have reduced the size of the data set sufficiently to make a logistic analysis unreliable. Nevertheless, one can predict that such a model might perhaps include variables describing the type and onset of the abdominal pain, stool guiac, and bowel sounds, in addition to a few select laboratory values.

SUMMARY

The clinical spectrum of intestinal ischemia ranges from relatively minor and reversible functional alterations of the intestinal mucosa to a massive hemorrhagic infarctions of the entire bowel carrying with it a prognosis of near certain death. Likewise, the clinical presentation is varied and the diagnosis is difficult. The classic presentation of the combination of sudden onset, severe, crampy, generalized abdominal pain accompanied by nausea and vomiting was found to be a common and valid diagnostic picture. Additionally, many patients were noted to have decreased serum bicarbonate, elevated glucose, and an amylase elevated out of proportion to lipase. Multiple air/fluid levels and dilated loops of small bowel were common on plain film diagnosis of the abdomen. While none of these findings is in itself specific for ischemic bowel, the combination of severe abdominal pain accompanied by any of the above should raise the level of suspicion of ischemia enough to warrant further radiographic studies. Lack of clinical suspicion, use of cardiac glycosides, and confounding illness in the aged patient all contributed significantly to delayed diagnosis. The use of a discriminant function may be valid as a diagnostic aid, but will need to be tested and enhanced with additional data collected prospectively.

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APPENDICES

APPENDIX A

ABDOMINAL PAIN PROTOCOL

Serial # - _____

PATIENT ID

Unit #: _____
Group: *ACUTE CHRONIC NOS CONTROL*
Age: ____
Sex: *MALE FEMALE*
Discharged *ALIVE DEAD*
Admitted to *MEDICINE SURGERY*

PAIN HISTORY

Time since onset _____ hrs.
At onset: *ASSOCIATED TRAUMA*
Site at onset: *RUQ RLQ LUQ LLQ UMB GENERALIZED*
Manner: *SUDDEN GRADUAL*
Intensity: *MILD MODERATE SEVERE*
Now
Site now: *RUQ RLQ LUQ LLQ UMB GENERALIZED*
Intensity: *MILD MODERATE SEVERE*
Quality: *CRAMPY SHARP*
Type: *INTERMITTENT CONSTANT*
Made better by: _____
Made worse by: _____
Associated pain: *FLANK SHOULDER THIGH CHEST*

ASSOCIATED SYMPTOMS

General *FEVER, CHILLS, SWEATS, HEADACHES, LIGHTHEADEDNESS*
GI *ANOREXIA, NAUSEA, VOMITING*
Vomiting: *BILIOUS, BLOOD, COFFEE GROUND*
Stool: *URGE TO DEFECATE, DIARRHEA BLOODY, BLACK*
Hrs since last movement: _____
Gynecological
LMP: _____
G___P___AB___

PAST MEDICAL HISTORY

Past similar episode: *YES NO*
Prior abdominal surgery: *YES NO*
Antecedent illness: _____
Clotting disorders: *ANTITHROMBIN III DEFICIENCY OTHER* _____
History of: *CIRRHOSIS, POLYCYTHEMIA VERA, SICKLE CELL DISEASE, CHF*
Medications: *CARDIAC GLYCOSIDES, ANTICOAGULANTS, ESTROGENS*
Cardiac: *RHEUMATIC HEART DISEASE*
Arrythmia: *A-FIB, OTHER* _____

PHYSICAL EXAM

Vital signs: T°___ P____
BP___/___ RR_____
General appearance
Motion: *STILL WRITHING*
Dehydration: *POOR TURGOR, DRY MEMBRANES*
Abdominal: *SCARS, DISTENTION*
Bowel sounds: *PRESENT or ABSENT, HYPERACTIVE, HIGH PITCHED*
Tenderness: *RUQ LUQ RLQ LLQ UMB GEN*
Signs: *REBOUND, GUARDING RIGIDITY, MURPHY'S, PSOAS, OBTURATOR, PAIN OUT OF PROPORTION*
Masses: *RUQ/LIVER, LUQ/SPLEEN, RLQ, LLQ, MIDLINE, PULSATILE*
Rectal: *HEME + +/-, PROSTATIC ENLARGEMENT, TENDERNESS*

LABORATORY

HCT _____
WBC
TOTAL _____
SEGS _____
BANDS _____
LYMPHS _____
MONOS _____
EOS _____
PLT _____
ABG
pH _____
BASE EXCESS _____
PT/PTT ___/___ . ___/___
URINALYSIS
WBC'S _____
RBC'S _____
AMYLASE _____
LIPASE _____
LFT'S
TOTAL BILI _____
SGOT _____
ALK PHOS _____
LDH _____
CPK _____
B PREG _____
PERITONEAL FLUID
GROSSLY POSITIVE,
RBC'S _____
WBC'S _____

EKG

Arrythmia: *A-FIB, OTHER* _____

RADIOLOGY

KUB _____

3-WAY *RIGID LOOP SIGN, THUMBPRINTING, FREE AIR, OTHER* _____

B ENEMA _____

B SWALLOW _____

ULTRASOUND _____

LIVER/SPLEEN SCAN *MESENTERIC BLUSH, OTHER* _____

IVP _____

HIDA SCAN _____

ARTERIOGRAM *BORDER BLUSH, REFLUX INTO AORTA, MESENTERIC ARTERY SPASM, THICK INTESTINAL WALL, POOR/NO VENOUS RETURN, OTHER* _____

CAT SCAN *GAS IN PORTAL SYSTEM, GAS IN MESENTERIC VEINS, GAS IN BOWEL WALL, OTHER* _____

INTERVENTION

Hours since presentation: _____
Type of intervention: _____

NOTES

_____
_____
_____
_____
_____
_____
_____
_____

30 CASES DELETED DUE TO MISSING DATA.
NUMBER OF CASES PROCESSED: 105

DEPENDENT VARIABLE MEANS

	AMY	HCO3	GLUCOSE
	4.182	3.147	173.240

ESTIMATES OF EFFECTS $B = (X'X)^{-1} X'Y$

		AMY	HCO3	GLUCOSE
CONSTANT		4.249	3.120	180.252
GRP	1	0.239	-0.097	25.390

STANDARDIZED ESTIMATES OF EFFECTS

		AMY	HCO3	GLUCOSE
CONSTANT		0.000	0.000	0.000
GRP	1	0.377	-0.332	0.236

TOTAL SUM OF PRODUCT MATRIX

	AMY	HCO3	GLUCOSE
AMY	39.191		
HCO3	-4.755	8.363	
GLUCOSE	-341.375	-840.926	1125077.152

RESIDUAL SUM OF PRODUCT MATRIX E'E = Y'Y-Y'XB

	AMY	HCO3	GLUCOSE
AMY	33.631		
HCO3	-2.492	7.442	
GLUCOSE	-930.969	-600.960	1062553.469

RESIDUAL COVARIANCE MATRIX S
Y.X

	AMY	HCO3	GLUCOSE
AMY	0.327		
HCO3	-0.024	0.072	
GLUCOSE	-9.039	-5.835	10316.053

RESIDUAL CORRELATION MATRIX R
Y.X

	AMY	HCO3	GLUCOSE
AMY	1.000		
HCO3	-0.158	1.000	
GLUCOSE	-0.156	-0.214	1.000

SQUARED MULTIPLE CORRELATIONS

AMY	HCO3	GLUCOSE
0.142	0.110	0.056

TEST FOR EFFECT CALLED:
GRP

NULL HYPOTHESIS CONTRAST AB

AMY	HCO3	GLUCOSE
0.239	-0.097	25.390

INVERSE CONTRAST $A(X'X)^{-1} A'$

0.010

HYPOTHESIS SUM OF PRODUCT MATRIX $H = B'A'(A(X'X)^{-1} A')^{-1} AB$

	AMY	HCO3	GLUCOSE
AMY	5.560		
HCO3	-2.263	0.921	
GLUCOSE	589.594	-239.966	62523.683

ERROR SUM OF PRODUCT MATRIX G = E'E

	AMY	HCO3	GLUCOSE
AMY	33.631		
HCO3	-2.492	7.442	
GLUCOSE	-930.969	-600.960	1062553.469

UNIVARIATE F TESTS

VARIABLE	SS	DF	MS	F	P
AMY	5.560	1	5.560	17.028	0.000
ERROR	33.631	103	0.327		
HCO3	0.921	1	0.921	12.747	0.001
ERROR	7.442	103	0.072		
GLUCOSE	62523.683	1	62523.683	6.061	0.015
ERROR	1062553.469	103	10316.053		

MULTIVARIATE TEST STATISTICS

WILKS' LAMBDA = 0.763
F-STATISTIC = 10.461 DF = 3, 101 PROB = 0.00

PILLAI TRACE = 0.237
F-STATISTIC = 10.461 DF = 3, 101 PROB = 0.00

HOTELLING-LAWLEY TRACE = 0.311
F-STATISTIC = 10.461 DF = 3, 101 PROB = 0.00

TEST OF RESIDUAL ROOTS

ROOTS 1 THROUGH 1
CHI-SQUARE STATISTIC = 27.463 DF = 3 PROB = 0.00

CANONICAL CORRELATIONS

0.487

DEPENDENT VARIABLE CANONICAL COEFFICIENTS
STANDARDIZED BY CONDITIONAL (WITHIN GROUPS) STANDARD DEVIATIONS

AMY	0.736
HCO3	-0.417
GLUCOSE	0.461

CANONICAL LOADINGS (CORRELATIONS BETWEEN CONDITIONAL DEPENDENT VARIABLES AND DEPENDENT CANONICAL FACTORS)

AMY	0.729
HCO3	-0.631
GLUCOSE	0.435

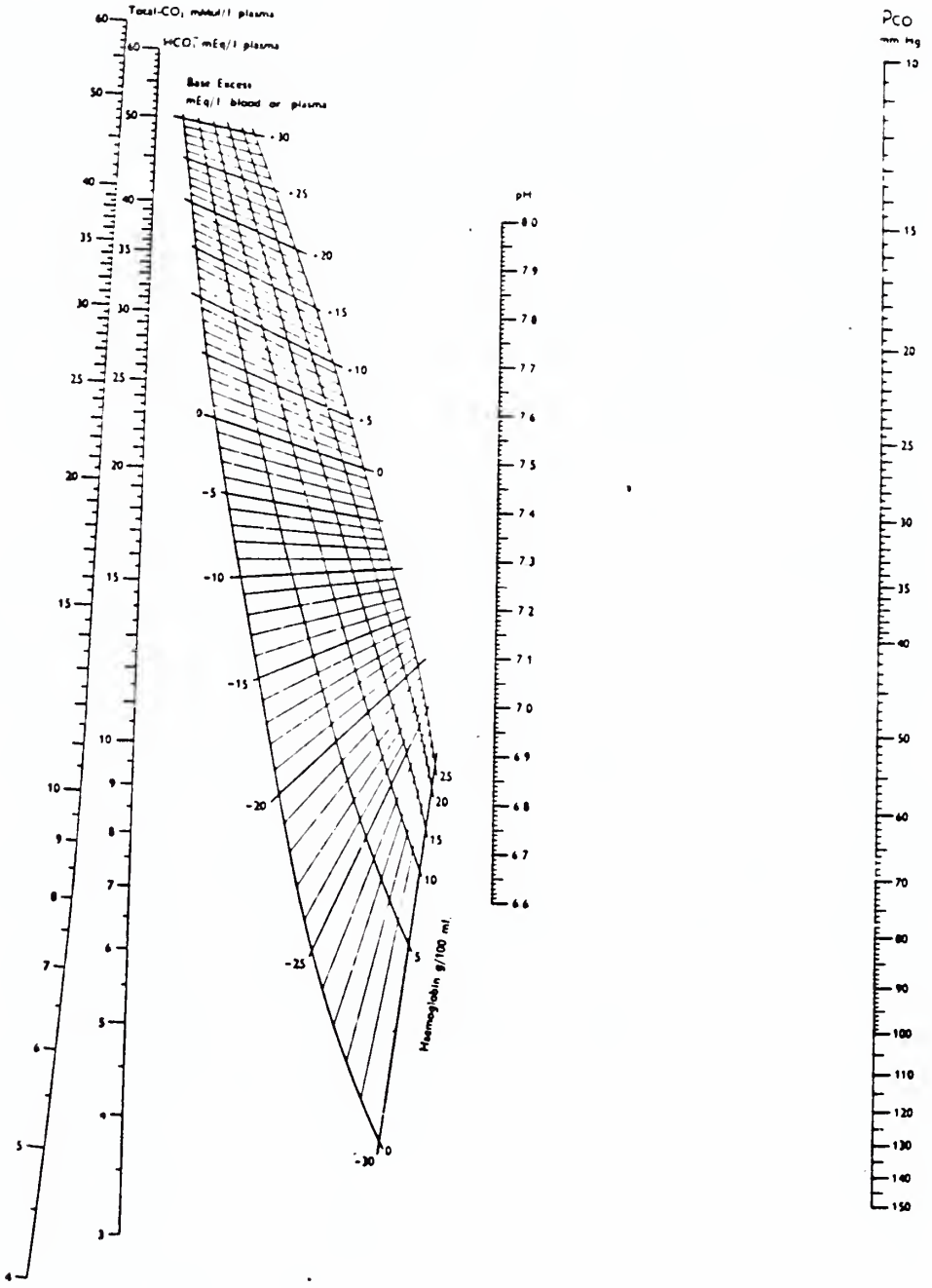
	1	2
AMY	19.607	18.129
HCO3	53.866	55.647
GLUCOSE	0.068	0.062
	1	2
	-133.059	-131.396

TABLE OF GROUP (ROWS) BY PREDICT (COLUMNS)

FREQUENCIES

	.	1	2	TOTAL
1	11	27	13	49
2	19	17	50	86
TOTAL	30	41	64	135

APPENDIX C



Siggard Andersen alignment nomogram for the determination of acid-base values of blood. From Siggard Anderson (1963) *Scand J Clin Lab Invest* 15, 211.

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